iMig 2021 wishes to warmly thank the following organizations for their generous support of the Meeting.

PLATINUM LEVEL

Bristol Myers Squibb

DIAMOND LEVEL

GOLD LEVEL

SUPPORTER LEVEL

COMMUNITY SUPPORTER
# TABLE OF CONTENTS

- iMig 2021 Sponsors ......................................................... 2
- Welcome Messages .......................................................... 4
- About iMig ........................................................................ 5

## MEETING INFORMATION

- Virtual Platform ................................................................. 7

## SCIENTIFIC PROGRAMME INFORMATION

- Programme at a Glance ...................................................... 9
- Scientific Programme
  - Sunday, May 2 .......................................................... 11
  - Friday, May 7 ........................................................... 13
  - Saturday, May 8 ......................................................... 16
  - Sunday, May 9 ........................................................... 23
  - Monday, May 10 ........................................................ 29
- Poster Listings ................................................................. 30
- Awards
  - iMig Wagner Medal .................................................... 42
  - iMig Research Award .................................................. 42
  - iMig Advancement Award ........................................... 42
  - Developing Nations Award ......................................... 42
  - Young Investigator Award .......................................... 43

## EXHIBITION INFORMATION

- Virtual Exhibit Information ................................................ 45

## ABSTRACT INFORMATION

- Abstract Listings ............................................................. 49
On behalf of the local organizing committee, we would like to extend you a warm welcome to the 5th Meeting of the International Mesothelioma Interest Group (iMig 2021) to be held as a virtual meeting. In 2020 and 2021, conferences around the world have been reshaped onto virtual platforms, and our meeting is, of course, one of these. Whilst we would have loved to have welcomed you to Brisbane, Australia last year, it was not to be. iMig 2020 was postponed at the last minute, as the global pandemic unfolded, and none of us had any idea what the next year would bring. It is important that our mesothelioma research and clinical community maintains our global connection, and although we cannot do this face to face, we are confident that our 2021 Virtual Meeting programme will be engaging and worthwhile.

Our multidisciplinary meeting brings together over 500 delegates from around the world, and features the most up-to-date research, diverse topics of interest and educational sessions with leading experts. We hope you will also take this opportunity to reach out to friends and colleagues in other ways for networking opportunities and to discuss research and collaboration. iMig 2021 provides the ideal impetus to start those conversations. We may also see iMig 2021 becoming more accessible to those who would not have been able to travel or those with time constraints, and we hope you will make the most of the chance to view expert presentations from sessions you may not have attended in person.
INTERNATIONAL MESOTHELIOMA INTEREST GROUP

The International Mesothelioma Interest Group (iMig) is an independent international group of scientists and clinicians working to understand, cure and prevent Mesothelioma. We invite you to become a member of iMig to strengthen our international voice and to improve the scientific exchange and knowledge about this malignancy.

Why Join iMig?
Membership is about communication and participation. Members will have access to all features of the iMig website (iMig.org) and opportunities to contribute content there. Via email, members will receive notices of updates to the website such as those involving upcoming meetings, funding or career opportunities, new presentations and research breakthroughs.

Although no membership dues are requested at this time, members are asked to participate in iMig by contributing to the website and/or participating in the biannual international meetings.

Finally, members help iMig by being part of our international community and showing their interest in understanding and ultimately preventing and defeating Mesothelioma.

iMig Officers 2018 – 2021

President:
Sam Armato, PhD, Chicago, United States

President-Elect:
Arnaud Scherpereel, MD, Lille, France

Secretary:
Jeremy Steele, MD, MRCP, London, United Kingdom

Treasurer:
Jim teWaterNaude, MD, Cape Town, South Africa

iMig Board Members 2018 – 2021

Courtney Broaddus, MD, San Francisco, United States
Raphael Bueno, MD, Boston, United States
Sjaak Burgers, MD, PhD, Amsterdam, The Netherlands
Dean Fennell, MD, PhD, Leicester, United Kingdom
Joseph Friedberg, MD, Baltimore, United States
Rabab Gaafar, MD, Cairo, Egypt
Marie-Claude Jaurand, PhD, Paris, France
Hedy Lee Kindler, MD, Chicago, United States
Luciano Mutti, MD, PhD, Philadelphia, United States
Takashi Nakano, MD, PhD, Osaka, Japan
Anna Nowak, MD, PhD, Perth, Australia
Isabelle Opitz, MD, Zurich, Switzerland
Andreas Rimner, MD, New York, United States
Bruce Robinson, MD, PhD, Perth, Australia
Yoshitaka Sekido, MD, PhD, Aichi, Japan
Walter Weder, MD, Zurich, Switzerland
Delegate Help Desk

The Attendee Experience Team will assist delegates with technical support and inquiries during the live broadcast days. For technical support and inquiries between April 29 – May 2, 2021 and May 3 – 7, 2021, please email iMig2021-registration@icsevents.com. The office is open Monday – Friday from 08:00 – 17:00 PDT (Pacific Daylight Time).

Certificate of Attendance

An email with a link to the post conference evaluation form will be sent to all registered delegates on May 9, 2021. Upon completing the evaluation form, the Certificate of Attendance will be emailed. If not received, please check your spam/junk folder. The deadline to complete the post conference evaluation is May 24, 2021.

CME Certificate

An email with a link to the post conference evaluation form will be sent to all registered delegates on May 9, 2021. Upon completing the evaluation form, the CME Certificate will be emailed on June 11, 2021. If not received, please check your spam/junk folder. The deadline to complete the post conference evaluation is May 24, 2021.

Disclaimer: The organizers have made every attempt to ensure all information in this publication is correct. The organizers take no responsibility for changes of the Programme or any loss that may occur as a result of changes on the Programme. Some of the information provided in this publication has been provided by external sources. Although every effort has been made to ensure accuracy, currency, and reliability of the content, the organizers accept no responsibility in that regard.
PROGRAMME

INFORMATION
# Programme at a Glance

## Sunday, May 2, 2021

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:00 AM - 6:30 AM</td>
<td>Pre-Conference Workshop: The Future of Mesothelioma - What Might the Next Decade Look Like For Our Patients?</td>
</tr>
<tr>
<td>1:00 PM - 3:30 PM</td>
<td>Pre-Conference Workshop: Mesothelioma in East Asia</td>
</tr>
<tr>
<td>1:00 PM - 3:30 PM</td>
<td>Pre-Conference Workshop: ITONF at iMig 2021 Nursing Workshop</td>
</tr>
</tbody>
</table>

## Friday, May 7, 2021

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:30 PM - 1:00 PM</td>
<td>Opening Session</td>
</tr>
<tr>
<td>1:00 PM - 2:30 PM</td>
<td>Plenary I: Origins of Mesothelioma</td>
</tr>
<tr>
<td>2:30 PM - 4:00 PM</td>
<td>Parallel Mini-Symposia 01: Pathology</td>
</tr>
<tr>
<td></td>
<td>Parallel Mini-Symposia 02: Clinical Trials</td>
</tr>
<tr>
<td></td>
<td>Parallel Mini-Symposia 03: Local and Intrapleural Therapies</td>
</tr>
</tbody>
</table>

## Saturday, May 8, 2021

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:30 AM - 2:00 AM</td>
<td>Parallel Mini-Symposia 04: Surgery</td>
</tr>
<tr>
<td></td>
<td>Parallel Mini-Symposia 05: Cell Therapies and Mesothelin Directed Therapies</td>
</tr>
<tr>
<td></td>
<td>Parallel Mini-Symposia 06: Nursing and Supportive Care</td>
</tr>
<tr>
<td></td>
<td>Parallel Mini-Symposia 07: Recent Developments: Genetics and Biomarkers</td>
</tr>
<tr>
<td>2:00 AM - 3:30 AM</td>
<td>Plenary II: Focus on the Patient</td>
</tr>
<tr>
<td>12:30 PM - 1:00 PM</td>
<td>Morning Session I</td>
</tr>
<tr>
<td>1:00 PM - 2:30 PM</td>
<td>Plenary III: Surgery – Individualising Care Appropriately</td>
</tr>
<tr>
<td>2:30 PM - 4:00 PM</td>
<td>Parallel Mini-Symposia 08: Immunotherapy and Checkpoint Blockade</td>
</tr>
<tr>
<td></td>
<td>Parallel Mini-Symposia 09: Peritoneal Mesothelioma</td>
</tr>
<tr>
<td></td>
<td>Parallel Mini-Symposia 10: Symptoms and Pleural Management</td>
</tr>
</tbody>
</table>
## Programme at a Glance

### Sunday, May 9, 2021

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:30 AM - 2:00 AM</td>
<td>Parallel Mini-Symposia 11: Biomarkers and Genetics</td>
</tr>
<tr>
<td></td>
<td>Parallel Mini-Symposia 12: Management Decisions in Mesothelioma</td>
</tr>
<tr>
<td></td>
<td>Parallel Mini-Symposia 13: Imaging</td>
</tr>
<tr>
<td>2:00 AM - 3:30 AM</td>
<td>Plenary IV: Immunotherapy - Checkpoint Blockade and Beyond</td>
</tr>
<tr>
<td>12:30 PM - 1:00 PM</td>
<td>Morning Session II</td>
</tr>
<tr>
<td>1:00 PM - 2:30 PM</td>
<td>Plenary V: Cutting Edge 2020</td>
</tr>
<tr>
<td>2:30 PM - 4:00 PM</td>
<td>Parallel Mini-Symposia 14: Biology and Novel Targets</td>
</tr>
<tr>
<td></td>
<td>Parallel Mini-Symposia 15: Epidemiology and Asbestos Control</td>
</tr>
<tr>
<td></td>
<td>Parallel Mini-Symposia 16: Biomarkers and Genetics II</td>
</tr>
</tbody>
</table>

### Monday, May 10, 2021

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:30 AM - 2:00 AM</td>
<td>Plenary VI: Towards Tomorrow</td>
</tr>
<tr>
<td>2:00 AM - 2:30 AM</td>
<td>Closing Session</td>
</tr>
</tbody>
</table>
**SCIENTIFIC PROGRAMME**

**Sunday, May 2, 2021**

*All times listed are in CEST (UTC +2) Time*

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>05:00 – 06:30</td>
<td><strong>PC01: Mesothelioma in East Asia</strong></td>
</tr>
<tr>
<td></td>
<td>Chairs: Ken Takahashi, Asbestos Diseases Research Institute, Australia</td>
</tr>
<tr>
<td></td>
<td>Takashi Kijima, Hyogo College of Medicine, Japan</td>
</tr>
<tr>
<td></td>
<td><strong>PC01.01: Keynote: Mesothelioma in East Asia “The Asian Mesothelioma Epidemic”</strong></td>
</tr>
<tr>
<td></td>
<td>Ken Takahashi, Asbestos Diseases Research Institute, Australia</td>
</tr>
<tr>
<td></td>
<td><strong>PC01.02: Hand-spining Chrysotile Exposure and Mesothelioma in Southeastern China</strong></td>
</tr>
<tr>
<td></td>
<td>Jianlin Lou, Zhejiang Academy of Medical Sciences, China</td>
</tr>
<tr>
<td></td>
<td><strong>PC01.03: Shipbreaking: Creating Accountability (199)</strong></td>
</tr>
<tr>
<td></td>
<td>Steven Kazan, Kazan, Mcclain, Satterley &amp; Greenwood, United States</td>
</tr>
<tr>
<td></td>
<td><strong>PC01.04: Nivolumab for Malignant Mesothelioma: A Real-world Experience (106)</strong></td>
</tr>
<tr>
<td></td>
<td>Takashi Kijima, Hyogo College of Medicine, Japan</td>
</tr>
<tr>
<td></td>
<td><strong>PC01.05: Malignant Pleural Mesothelioma of the Women in Our Hospital (264)</strong></td>
</tr>
<tr>
<td></td>
<td>Kohei Ando, Yokosuka Kyosai Hospital, Japan</td>
</tr>
<tr>
<td></td>
<td>Live Q&amp;A</td>
</tr>
<tr>
<td>13:00 – 15:30</td>
<td><strong>PC02: ITONF at iMig 2021 Nursing Workshop</strong></td>
</tr>
<tr>
<td></td>
<td>Chairs: Maria Guerin, Liverpool University Foundation Trust, United Kingdom</td>
</tr>
<tr>
<td></td>
<td>Kenneth O’Byrne, QUT - Cancer &amp; Ageing Research Program, Australia</td>
</tr>
<tr>
<td></td>
<td><strong>PC02.01: Global Nursing Models: An Overview of Nursing in Mesothelioma</strong></td>
</tr>
<tr>
<td></td>
<td>Melissa Culligan, Univ of Maryland Medical Center, United States</td>
</tr>
<tr>
<td></td>
<td><strong>PC02.02: Decision Making in Mesothelioma</strong></td>
</tr>
<tr>
<td></td>
<td>Zoe Davey, Oxford Brookes University, United Kingdom</td>
</tr>
<tr>
<td></td>
<td><strong>PC02.03: The Clinical Trial Landscape in Mesothelioma</strong></td>
</tr>
<tr>
<td></td>
<td>Buerkley Rose, University of Chicago, United States</td>
</tr>
<tr>
<td></td>
<td><strong>PC02.04: Case Study: Global Perspectives: Presentation, Treatment &amp; Care Including the Medico-Legal Aspects</strong></td>
</tr>
<tr>
<td></td>
<td>Liz Darlison, Mesothelioma UK/Univ Hospitals of Leicester, United Kingdom</td>
</tr>
<tr>
<td></td>
<td>Jocelyn McLean, Asbestos Diseases Research Institute, Australia</td>
</tr>
<tr>
<td></td>
<td>Buerkley Rose, University of Chicago, United States</td>
</tr>
<tr>
<td></td>
<td>Lorraine Creech, Mesothelioma UK, United Kingdom</td>
</tr>
<tr>
<td></td>
<td>14:15 Break</td>
</tr>
</tbody>
</table>
**Sunday, May 2, 2021**

*All times listed are in CEST (UTC +2) Time*

<table>
<thead>
<tr>
<th><strong>PC02.05</strong>: Evaluation of Mesothelioma in a Large District General Hospital in the UK 2017 - 2018. A Retrospective Case Note Audit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anne Moylan, Portsmouth Hospitals NHS Trust, United Kingdom</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PC02.06</strong>: What are the Psychological Effects of Mesothelioma on Patients &amp; Their Carers? A Scoping Collaboration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virginia Sherborne, University of Sheffield, United Kingdom</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PC02.07</strong>: Supporting Our Armed Forces. Raising Awareness and Providing Information and Support for Veterans/Armed Forces Personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helen Wilkes, Mesothelioma UK/NHS, United Kingdom</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PC02.08</strong>: Non-NHS Funded Therapy vs Clinical Trials: The Importance of Patient Autonomy in Mesothelioma Treatment Decision Making</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon Bolton, Calderdale &amp; Huddersfield NHS Foundation Trust, United Kingdom</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PC02.09</strong>: MAGS: The Healthcare Staff Mesothelioma Asbestos Guidance Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angela Tod, University of Sheffield, United Kingdom</td>
</tr>
</tbody>
</table>

**Live Q&A**

**On-Demand Workshop**

<table>
<thead>
<tr>
<th><strong>PC03</strong>: The Future of Mesothelioma - What Might the Next Decade Look Like for Our Patients?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chairs: Bruce Robinson, University of Western Australia, Australia</td>
</tr>
<tr>
<td>Michele Carbone, University of Hawaii Cancer Center, United States</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PC03.01</strong>: The Future of Mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dean Fennell, University of Leicester, United Kingdom</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PC03.02</strong>: Genomics: How Understanding the Genetics of Mesothelioma May Help with Prevention and Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michele Carbone, University of Hawaii Cancer Center, United States</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PC03.03</strong>: Immunology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruce Robinson, University of Western Australia, Australia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PC03.04</strong>: The Future of Mesothelioma - A Functional Genomics Standpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wee Loong (Melvin) Chin, NCARD, Australia</td>
</tr>
</tbody>
</table>
### Friday, May 7, 2021

All times listed are in CEST (UTC +2) Time

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:30 – 13:00</td>
<td>Opening Session</td>
</tr>
<tr>
<td>13:00 – 14:30</td>
<td><strong>PL01: Plenary I: Origins of Mesothelioma</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Track: Epidemiology, Pathology, Mesothelioma Biology and Novel Targets</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Chairs:</strong> Ken Takahashi, Asbestos Diseases Research Institute, Australia</td>
</tr>
<tr>
<td></td>
<td>Jim TeWaterNaude, Diagnostic Medicine &amp; University of Cape Town, South Africa</td>
</tr>
<tr>
<td></td>
<td><strong>PL01.01:</strong> The Global Mesothelioma Epidemic and Control Strategies</td>
</tr>
<tr>
<td></td>
<td>Ken Takahashi, Asbestos Diseases Research Institute, Australia</td>
</tr>
<tr>
<td></td>
<td><strong>PL01.02:</strong> Mesothelioma in Situ</td>
</tr>
<tr>
<td></td>
<td>Sonja Klebe, Flinders University &amp; SA Pathology, Australia</td>
</tr>
<tr>
<td></td>
<td><strong>PL01.03:</strong> Germline and Somatic Mutations in Mesothelioma</td>
</tr>
<tr>
<td></td>
<td>Jane Churpek, The University of Wisconsin-Madison, United States</td>
</tr>
<tr>
<td></td>
<td><strong>PL01.04:</strong> Spatial Intra-Tumor Molecular Heterogeneity in Malignant Pleural Mesothelioma</td>
</tr>
<tr>
<td></td>
<td>Didier Jean, Inserm - Centre de Recherche des Cordeliers, France</td>
</tr>
<tr>
<td></td>
<td><strong>PL01.05:</strong> The MexTAg Collaborative Cross: Identifying the Genetic Basis of Mesothelioma. An Interim Report</td>
</tr>
<tr>
<td></td>
<td>Scott Fisher, The University of Western Australia, Australia</td>
</tr>
<tr>
<td></td>
<td><strong>PL01.06:</strong> Multiple Cancers in 416 Patients with Malignant Mesothelioma</td>
</tr>
<tr>
<td></td>
<td>Vasiliki Panou, Odense University Hospital, Denmark</td>
</tr>
<tr>
<td></td>
<td><strong>PL01.07:</strong> Asbestos Induces Mesothelial Cell Transformation via HMGB1-Driven Autophagy</td>
</tr>
<tr>
<td></td>
<td>Haining Yang, University of Hawaii Cancer Center, United States</td>
</tr>
<tr>
<td></td>
<td>Live Q&amp;A</td>
</tr>
<tr>
<td>14:30 – 16:00</td>
<td><strong>MS01: Parallel Mini-Symposia 01: Pathology</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Track: Pathology</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Chairs:</strong> Sonja Klebe, Flinders University &amp; SA Pathology, Australia</td>
</tr>
<tr>
<td></td>
<td>Marie-Claude Jaurand, INSERM, France</td>
</tr>
<tr>
<td></td>
<td><strong>MS01.01:</strong> As Pathologist What Have We Learned from Deep Learning for the Diagnostic or Pronostic of Mesothelioma</td>
</tr>
<tr>
<td></td>
<td>Francoise Galateau-Salle, Mesopath Cancer Center Leon Berard, France</td>
</tr>
<tr>
<td></td>
<td><strong>MS01.03:</strong> Differential Diagnosis of Biphasic Malignant Pleural Mesothelioma on Pleural Effusions by Gene Expression</td>
</tr>
<tr>
<td></td>
<td>Rossella Bruno, University Hospital of Pisa, Italy</td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>14:30 – 16:00</td>
<td>MS02: Parallel Mini-Symposia 02: Clinical Trials</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**MS02.06:** Phase II Study of PARP Inhibitor Olaparib in Patients with Malignant Mesothelioma  
Raffit Hassan, National Cancer Institute, United States

**MS02.07:** Searching for Enrolment for MARS-2: A United Kingdom Cancer Network’s Specialist Mesothelioma MDT Screening Experience  
John Edwards, Sheffield Teaching Hospitals NHS Fdn Trust, United Kingdom

**MS02.08:** First-Line Nivolumab Plus Ipilimumab Versus Chemotherapy in Unresectable Malignant Pleural Mesothelioma (MPM) in CheckMate 743  
Sanjay Popat, Royal Marsden Hospital, United Kingdom

**Live Q&A**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
<th>Speaker &amp; Institution</th>
</tr>
</thead>
</table>
| 14:30 – 16:00 | **MS03:** Parallel Mini-Symposia 03: Local and Intrapleural Therapies | **Track:** Radiation Oncology, Surgery  
**Chairs:** Robert Rintoul, University of Cambridge, United Kingdom  
Gavin Wright, St Vincent’s Hospital Melbourne, Australia |
| **MS03.01:** Where Are the Intrapleural Therapies? | Daniel Sterman, NYU Langone Health, United States |
| **MS03.02:** Take or Spare the Lung for Low Volume Stage I Disease - Is There a Correct Approach? | Joseph Friedberg, Univ of Maryland Medical Center, United States |
| **MS03.03:** Proton Therapies for Mesothelioma | Charles Simone, New York Proton Center, United States |
| **MS03.04:** Where There’s a TIL, There’s a Ray: Image Guided X-rays Induce Changes in T-cell Phenotypes in Mesothelioma Tumour Micro-environments | Wesley Wilson, National Centre for Asbestos Related Diseases, Canada |
| **MS03.05:** Treatment of Lung-Intact Malignant Pleural Mesothelioma with Whole Pleural Intensity-Modulated Proton Therapy: Toxicities and Clinical Outcomes | Jason Molitoris, Univ of Maryland/Maryland Proton Treatment Ctr, United States |
| **MS03.06:** Effects of Photon Radiation on DNA Damage, Cell Cycle, Cell Proliferation, and Apoptosis in Murine and Human Mesothelioma Cell Lines | Synat Keam, NCARD, Australia |
| **MS03.07:** Does Sparing the Diaphragm Improve Early Outcome From Radical Surgery For Malignant Pleural Mesothelioma? | Michelle Lee, Barts Thorax Centre, United Kingdom |

**Live Q&A**
### Saturday, May 8, 2021

All times listed are in CEST (UTC +2) Time

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Details</th>
</tr>
</thead>
</table>
| 00:30 – 02:00 | **MS04: Parallel Mini-Symposia 04: Surgery**                                                | *Track: Surgery*  
Chairs: Marc De Perrot, University Health Network (UHN), Canada  
Andrea Wolf, The Icahn School of Medicine at Mount Sinai, United States |
|          | **MS04.01: Ultimate Patient Selection**                                                     | Seiki Hasegawa, Hyogo College of Medicine, Japan                        |
|          | **MS04.02: Complete Resection in Mesothelioma**                                            | Naveed Alam, St Vincent’s Hospital, Australia                           |
|          | **MS04.03: Has the Toronto SMART Protocol Resurrected EPP? Should This Be the Only Indication?** | Marc De Perrot, University Health Network (UHN), Canada                 |
|          | **MS04.04: Efficacy of Irradiation Combined with Intracavitary Cisplatin-fibrin After Lung-sparing Surgery in an Orthotopic Rat Model of Mesothelioma** | Michaela Kirschner, University Hospital Zurich, Switzerland              |
|          | **MS04.05: Utilizing Endobronchial Ultrasound for Mediastinal Staging in Pleural Mesothelioma** | Desiree Steimer, Brigham and Women's Hospital, United States             |
|          | **MS04.06: Anti-PD-1 Therapy after Multimodality Therapy Including Total Pleurectomy in Malignant Pleural Mesothelioma: Updated Analysis** | Loic Lang-Lazdunski, Institut Universitaire de Cardiologie et Pneumologie de Quebec, Canada |
|          | **MS04.07: Postoperative Empyema after Pleurectomy Decortication for Malignant Pleural Mesothelioma** | Moshe Lapidot, Brigham and Women’s Hospital, United States              |
|          | **Live Q&A**                                                                              |                                                                        |

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Details</th>
</tr>
</thead>
</table>
| 00:30 – 02:00 | **MS05: Parallel Mini-Symposia 05: Cell Therapies and Mesothelin Directed Therapies**       | *Track: Biomarkers, Genetics/Bioinformatics, Immunology, Nursing and Allied Health*  
Chairs: Steven Kao, Chris O'Brien Lifehouse, Australia  
Nick Pavlakis, Royal North Shore Hospital, Australia |
|          | **MS05.01: Mesothelioma as a Target for Adoptive T Cell Therapy/T Cell Therapies and Vaccine** | Edmund Moon, University of Pennsylvania, United States                 |
|          | **MS05.02: Mesothelin Targeted Therapy**                                                    | Raffit Hassan, National Cancer Institute, United States                |
|          | **MS05.03: What's All the Buzz about Car-T in the US? About Car-T, Patient Care, Toxicities, and Nursing Considerations for Pleural and Peritoneal Patients** | Ali Massey, Memorial Sloan Kettering Cancer Center, United States       |
### MS05.04: Analysis and Augmentation of the Immunologic Bystander Effects of CAR T Cells in a Malignant Mesothelioma (MM) Syngeneic Mouse Model
Astero Klampatsa, Institute of Cancer Research, United Kingdom

### MS05.05: Regional Delivery of CAR T Cells with Cell-intrinsic Checkpoint Blockade Eradicates Malignant Pleural Mesothelioma: Rationale for Clinical Trial
Hue Quach, Memorial Sloan Kettering, United States

### MS05.06: Examining the Interaction of Mesothelin and CA125 in Malignant Pleural Mesothelioma
Alistair Nash, NCARD, University of Western Australia, Australia

### MS05.07: Engineering Chimeric Antigen Receptor T Cells to Secrete Fucosyltransferase Augments Cutaneous Lymphocyte Antigen Expression and Infiltration into Mesothelin Positive Tumors
Edmund Moon, University of Pennsylvania, United States

### Live Q&A

### 00:30 – 02:00

#### MS06: Parallel Mini-Symposia 06: Nursing and Supportive Care
**Track: Nursing and Allied Health**

- **Chairs:** Liz Darlison, Mesothelioma UK/Univ Hospitals of Leicester, United Kingdom
  Buerkley Rose, University of Chicago, United States

#### MS06.01: Patient Experiences in the MARS 2 Study
Angela Tod, University of Sheffield, United Kingdom

#### MS06.03: Body Composition, Diet and Exercise in People with Mesothelioma
Carolyn McIntyre, Edith Cowan University, Australia

#### MS06.04: Post-traumatic Stress as Asbestos Victim among Bereaved of Patients with Malignant Pleural Mesothelioma in Japan
Sarah Yasuko Nagamatsu, St. Luke’s International University, Japan

#### MS06.05: Patient and Informal Carers Experience of Living with Mesothelioma: A Systematic Rapid Review and Synthesis of the Literature
Stephanie Ejegi-Memeh, School of Nursing and Midwifery, United Kingdom

#### MS06.06: Development of Mesothelioma Care Passport
Maria Guerin, Liverpool University Foundation Trust, United Kingdom

#### MS06.07: The Impact of the COVID-19 Pandemic on the Experiences of People with Mesothelioma and Their Informal Carers in the UK: Recommendations for Practice
Bethany Taylor, University of Sheffield, United Kingdom

### Live Q&A
<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Speaker/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS07: Parallel Mini-Symposia 07: Recent Developments: Genetics and Biomarkers</strong>&lt;br&gt;<strong>Track: Biomarkers, Genetics/Bioinformatics, Mesothelioma Biology and Novel Targets</strong>&lt;br&gt;<strong>Chairs: Didier Jean, Inserm - Centre de Recherche des Cordeliers, France</strong></td>
<td></td>
</tr>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS07.01: Assessment of Potential Predictors of Calretinin and Mesothelin Plasma Levels to Improve the Diagnostic Performance to Detect Malignant Mesothelioma</strong>&lt;br&gt;Swaantje Casjens, Inst for Prevention &amp; Occupational Medicine of the German Social Accident Insurance (IPA), Germany</td>
<td></td>
</tr>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS07.02: Biallelic Inactivation of Tumor Suppressor Genes in Mesothelioma Involving Balanced Translocations</strong>&lt;br&gt;James Smadbeck, Mayo Clinic, United States</td>
<td></td>
</tr>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS07.03: Calretinin and Mesothelin for the Early Detection of Mesothelioma – Results of the MoMar Cohort</strong>&lt;br&gt;Georg Johnen, Inst for Prevention &amp; Occupational Medicine of the German Social Accident Insurance (IPA), Germany</td>
<td></td>
</tr>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS07.04: Genomic and Transcriptomic Profiling of Malignant Mesothelioma Patients Identifies Gene Signatures Predictive of Survival and Response to Immuno and Chemotherapy</strong>&lt;br&gt;Nishanth Nair, National Cancer Institute, NIH, United States</td>
<td></td>
</tr>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS07.05: Importance of Cullin4 Ubiquitin Ligase in Malignant Pleural Mesothelioma</strong>&lt;br&gt;Mayura Meerang, Dept of Thoracic Surgery, University Hospital Zürich, Switzerland</td>
<td></td>
</tr>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS07.06: Inactivation of the BAP1 Tumour Suppressor in Mesothelioma Suppresses Expression of the 14q32.31 miRNA Locus, Contributing to the Cancer Phenotype</strong>&lt;br&gt;Martina Tripari, University of Liverpool, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS07.07: Optimizing Survival Prediction in Malignant Mesothelioma; Development and External Validation of a Clinical Prediction Model (MESOPRO)</strong>&lt;br&gt;Corneinde Jannette de Gooijer, Netherlands Cancer Institute, Netherlands</td>
<td></td>
</tr>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS07.08: Blood and FBLN3: Be Careful How and What You Collect</strong>&lt;br&gt;Harvey Pass, NYU Langone Medical Center, United States</td>
<td></td>
</tr>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS07.09: Malignant Pleural Mesothelioma: Germline Variants May Steer Tailored Treatment</strong>&lt;br&gt;Marika Sculco, Università Del Piemonte Orientale, Italy</td>
<td></td>
</tr>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS07.10: Malignant Pleural Mesothelioma with Genomic Near-Haploidization: A Newly Recognized Subset with Distinct Histologic, Clinical, and Genomic Features</strong>&lt;br&gt;Soo-Ryum Yang, Memorial Sloan Kettering Cancer Center, United States</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Live Q&amp;A</strong></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
<td>Track</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>02:00 – 03:30</td>
<td><strong>PL02: Plenary II: Focus on the Patient</strong></td>
<td><strong>Track: Symptom Management/Pleural Management, Clinical Trials, Nursing and Allied Health</strong></td>
</tr>
<tr>
<td></td>
<td><strong>PL02.01: Surgical Approaches for Managing Symptoms in Pleural Disease</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>PL02.02: The IPC - Now Standard Care?</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>PL02.03: Switch Maintenance Gemcitabine after First Line Chemotherapy in Patients with Malignant Mesothelioma; Updated Results of a Multicenter Open Label Phase II Trial (NVALT19)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>PL02.04: Impact and Inequalities: Findings from the Military Experiences of Mesothelioma Study</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Live Q&amp;A</td>
<td></td>
</tr>
<tr>
<td>12:30 – 01:00</td>
<td><strong>SS01: Morning Session I</strong></td>
<td><strong>Track: N.A.</strong></td>
</tr>
<tr>
<td></td>
<td><strong>SS01.01: International Association for the Study of Lung Cancer (IASLC)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>SS01.02: Mesothelioma UK</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>SS01.03: L’association France-Mésothéliome</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>SS01.04: International Thoracic Oncology Nursing Forum</strong></td>
<td></td>
</tr>
</tbody>
</table>
### 13:00 – 14:30

**PL03: Plenary III: Surgery – Individualising Care Appropriately**
**Track: Surgery, Nursing and Allied Health, Clinical Trials**
**Chairs:** Joseph Friedberg, Univ of Maryland Medical Center, United States
Walter Weder, Thoraxchirurgie-Bethanien, Switzerland

**PL03.01:** Is Biphasic an Independent Entity or Do We Need Extensive Sampling to Predict the % of Sarcomatoid Which May Influence Selection
Francoise Galateau-Salle, Mesopath Cancer Center Leon Berard, France

**PL03.02:** Can Surgery Be Delayed or Avoided Altogether in Patients with Good Response to Induction Chemotherapy, Especially in Elderly Patients?
Isabelle Opitz, University Hospital Zurich, Switzerland

**PL03.03:** The Surgical Patient, Trials, Care, Support, Outcomes?
Melissa Culligan, Univ of Maryland Medical Center, United States

**PL03.04:** Window of Opportunity in Immunotherapy
Boris Sepesi, The University of Texas Md Anderson Cancer Center, United States

**PL03.05:** The Role of Serum Mesothelin in Monitoring Patients Following Extended Pleurectomy Decortication for Malignant Pleural Mesothelioma: An Interim Analysis
Alan Dawson, University Hospitals of Leicester, United Kingdom

**PL03.06:** Project 1 Surgical Mesothelioma Consortium: Long Term Survivor
Isabelle Opitz, University Hospital Zurich, Switzerland

**Live Q&A**

### 14:30 – 16:00

**MS08: Parallel Mini-Symposia 08: Immunotherapy and Checkpoint Blockade**
**Track: Immunology, Biomarkers, Genetics/Bioinformatics**
**Chairs:** Joost Lesterhuis, NCARD, Australia
Luciano Mutti, Temple University, United Kingdom

**MS08.01:** Immunotherapy Targets Moving Forward
Luana Calabro, University Hospital of Siena, Italy

**MS08.02:** Biomarkers for Immunotherapy in Mesothelioma
Joachim Aerts, Erasmus University Medical Center, Netherlands

**MS08.03:** Epigenetic Remodelling to Improve the Efficacy of Immunotherapy
Alessia Covre, University Hospital of Siena, Italy

**MS08.04:** Tumour-Specific Effector Memory Cytotoxic T Lymphocytes (CTL) Associates with Successful Outcomes to Immune Checkpoint Blockade in a Murine Mesothelioma Model
Nicola Principe, NCARD/UWA, Australia
### Saturday, May 8, 2021

All times listed are in CEST (UTC +2) Time

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MS08.05</strong></td>
<td>High PD-L1 (CD274) RNA Expression is Associated with Diverse Transcriptional Phenotypes in Malignant Pleural Mesothelioma</td>
<td>Benjamin Wadowski, Brigham and Women's Hospital, United States</td>
</tr>
<tr>
<td><strong>MS08.06</strong></td>
<td>Targeting Small Pleural Macrophages in an Intrathoracic Murine Malignant Pleural Mesothelioma Model</td>
<td>Mikihiro Kohno, University Health Network, Canada</td>
</tr>
<tr>
<td><strong>MS09.01</strong></td>
<td>Peritoneal Debulking Surgery</td>
<td>Nicholas Lutton, Princess Alexandra Hospital, Brisbane Australia, Australia</td>
</tr>
<tr>
<td><strong>MS09.02</strong></td>
<td>Does HIPEC Have a Role in Management of Intraperitoneal Disease</td>
<td>Tom Cecil, PMI, United Kingdom</td>
</tr>
<tr>
<td><strong>MS09.03</strong></td>
<td>Immunotherapy and Immunochemotherapy in Peritoneal Mesothelioma</td>
<td>Kenneth O’Byrne, QUT - Cancer &amp; Ageing Research Program, Australia</td>
</tr>
<tr>
<td><strong>MS09.04</strong></td>
<td>Interim Results of Phase II Trial for Novel Magnetic Resonance Imaging of Peritoneal Mesothelioma</td>
<td>Ankit Dhiman, University of Chicago, United States</td>
</tr>
<tr>
<td><strong>MS09.05</strong></td>
<td>Bap1+/- GEM Mice Exposed to Minimal Doses of Crocidolite or Chrysotile Asbestos Exhibit Increased Susceptibility to Peritoneal Mesothelioma Induction</td>
<td>Yuwaraj Kadariya, Fox Chase Cancer Center, United States</td>
</tr>
<tr>
<td><strong>MS09.06</strong></td>
<td>Molecular Characterization of Peritoneal Mesotheliomas</td>
<td>Michael Offin, Memorial Sloan Kettering Cancer Center, United States</td>
</tr>
<tr>
<td><strong>MS09.07</strong></td>
<td>Outcomes in 40 Patients with Multicystic Peritoneal Mesothelioma Treated by Cytoreductive Surgery and Hyperthermic Intra-abdominal Chemotherapy</td>
<td>Assad Zahid, Peritoneal Malignancy Inst, Basingstoke Hosp UK, Australia</td>
</tr>
<tr>
<td><strong>MS09.08</strong></td>
<td>Surgical Phenotype of Patients with Malignant Peritoneal Mesothelioma and a Germline Mutation</td>
<td>Yaniv Berger, Chaim Sheba Medical Center, Israel</td>
</tr>
<tr>
<td><strong>MS09.09</strong></td>
<td>Peritoneal Mesothelioma: Improving Outcome Measures Through National Audit in England</td>
<td>Susan Harden, Ntl Mesothelioma Audit, Royal College of Physicians, United Kingdom</td>
</tr>
</tbody>
</table>

**Live Q&A**
<table>
<thead>
<tr>
<th>Time</th>
<th>Session Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:30 – 16:00</td>
<td><strong>MS010: Parallel Mini-Symposia 09: Peritoneal Mesothelioma</strong>&lt;br&gt;<strong>Track:</strong> Peritoneal Mesothelioma, Mesothelioma Biology and Novel Targets, Clinical Trials&lt;br&gt;<strong>Chairs:</strong> Sanjeev Naidu, Mater &amp; Princess Alexandra Hospitals, Australia</td>
</tr>
<tr>
<td><strong>MS10.01:</strong> Symptom Burden in Mesothelioma - Pharmacological and Non-pharmacological Management</td>
<td>David Currow, Cancer Institute NSW, Australia</td>
</tr>
<tr>
<td><strong>MS10.02:</strong> Pleurodesis - Updates and Advances</td>
<td>Nick Maskell, University of Bristol, United Kingdom</td>
</tr>
<tr>
<td><strong>MS10.03:</strong> The Role of the Clinical Nurse Specialist in the Patient Journey</td>
<td>Lorraine Creech, Mesothelioma UK, United Kingdom</td>
</tr>
<tr>
<td><strong>MS10.04:</strong> Symptom Burden and Unmet Needs in MPM: Exploratory Analyses from the RESPECT-Meso Study</td>
<td>Siao Nge Hoon, Sir Charles Gairdner Hospital, Australia</td>
</tr>
<tr>
<td><strong>MS10.05:</strong> Retrospective Study on Decision Tree Analysis Prognostic Scores in Malignant Pleural Mesothelioma - a DGH UK Perspective</td>
<td>Pradeep Rajagopalan, Barts And Royal London Hospital, United Kingdom</td>
</tr>
<tr>
<td><strong>MS10.06:</strong> Improving Survival Is Not the Only Relevant Outcome for Patients Suffering from Malignant Pleural Mesothelioma and Their Caregivers: An Explorative Study (PointInMe_Explor)</td>
<td>Federica Grosso, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Italy</td>
</tr>
<tr>
<td><strong>MS10.07:</strong> An Integrative Systematic Review Exploring the Palliative Care Needs of Patients with Mesothelioma and Their Carers</td>
<td>Clare Gardiner, University of Sheffield, United Kingdom</td>
</tr>
<tr>
<td></td>
<td>Live Q&amp;A</td>
</tr>
</tbody>
</table>
# SCIENTIFIC PROGRAMME

## Sunday, May 9, 2021

*All times listed are in CEST (UTC +2) Time*

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Track</th>
<th>Chairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS011: Parallel Mini-Symposia 11: Biomarkers and Genetics</strong>&lt;br&gt;<strong>Track:</strong> Biomarkers, Genetics/Bioinformatics, Mesothelioma Biology and Novel Targets&lt;br&gt;<strong>Chairs:</strong> Jenette Creaney, NCARD UWA, Australia&lt;br&gt;Glen Reid, Dunedin School of Medicine, New Zealand</td>
<td><strong>MS11.01:</strong> RNA as a Biomarker&lt;br&gt;Oluf Røe, Norwegian Univ of Science &amp; Technology, Norway</td>
<td><strong>MS11.02:</strong> Mitochondrial Mechanisms of Therapy Resistance: New Bio-markers in Aggressive Cancer&lt;br&gt;Michelangelo Campanella, University of London, United Kingdom</td>
</tr>
<tr>
<td></td>
<td><strong>MS11.03:</strong> miRNA in Mesothelioma&lt;br&gt;Glen Reid, Dunedin School of Medicine, New Zealand</td>
<td><strong>MS11.04:</strong> Chromosomal Rearrangements and Neoantigen Expression&lt;br&gt;Tobias Peikert, Mayo Clinic, Rochester, United States</td>
<td><strong>MS11.05:</strong> MESOMICS Project: Deep Genomic Characterisation and Integration Unveil Specific Cancer Tasks and Evolutionary Traits, Together with Specific Morphological and Molecular Profiles with Important Clinical Implications&lt;br&gt;Lise Mangiante, International Agency for Research on Cancer - WHO, France</td>
</tr>
<tr>
<td></td>
<td><strong>MS11.06:</strong> Extracellular Vesicles as Novel Biomarkers in Malignant Pleural Mesothelioma&lt;br&gt;Tamkin Ahmadzada, The University of Sydney, Australia</td>
<td><strong>MS11.07:</strong> Circular RNA as a Biomarker for Malignant Pleural Mesothelioma&lt;br&gt;Ben Johnson, Asbestos Diseases Research Institute, Australia</td>
<td><strong>Live Q&amp;A</strong></td>
</tr>
<tr>
<td>00:30 – 02:00</td>
<td><strong>MS012: Parallel Mini-Symposia 12: Management Decisions in Mesothelioma</strong>&lt;br&gt;<strong>Track:</strong> Pathology, Nursing and Allied Health, Biomarkers, Genetics/Bioinformatics, Clinical Trials, Surgery, Epidemiology and Asbestos Control&lt;br&gt;<strong>Chairs:</strong> Edwina Duhig, Sullivan Nicolaides Pathology, Australia&lt;br&gt;Jeremy Steele, St Bartholomew's Hospital, United Kingdom</td>
<td><strong>MS12.01:</strong> The Impact of Histopathological Subtypes of Mesothelioma on Decision Making for Systemic and Immunotherapy in 2020&lt;br&gt;Jennifer Sauter, Memorial Sloan Kettering Cancer Ctr, United States</td>
<td><strong>MS12.02:</strong> Mesothelioma Patients’ Experiences of Follow-up Care&lt;br&gt;Zoe Davey, Oxford Brookes University, United Kingdom</td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 00:30 – 02:00 | **MS013: Parallel Mini-Symposia 13: Imaging**  
Track: Imaging, Clinical Trials  
Chairs: Sam Armato, The University of Chicago, United States  
Ritu Gill, Harvard Medical School, United States |
| MS12.04: Predictive Role of Soluble Levels of PD-L1 in Mesothelioma Patients from the NIBIT-MESO-1 Study | Alessia Covre, University Hospital of Siena, Italy |
| MS12.05: Priorities of People with Mesothelioma: A Qualitative Study of Trial Participation and Treatment Decisions | Anna Bibby, Bristol Academic Respiratory Unit, United Kingdom |
| MS12.06: How Much Do We Actually Know Before Embarking on Radical Surgery for Mesothelioma? – the Multidisciplinary Implications for Preoperative Work Up | Ralitsa Baranowski, Barts Health NHS Trust, United Kingdom |
| MS12.07: Mesothelioma in a Developing Country: The Long Path of Patients Inside Health Care Systems to Proper Diagnosis and Management | Paulo Gregorio, Sao Paulo Cancer Institute - São Paulo University, Brazil |
| Live Q&A | |
| MS13.01: Mesothelioma Staging Update | Anna Nowak, NCARD, Australia |
| MS13.02: Assessment of Apparent Diffusion Coefficient in Biphasic Malignant Pleural Mesothelioma from Diffusion Weighted MRI (DWI) | Ritu Gill, Harvard Medical School, United States |
| MS13.03: A Comparison of Magnetic Resonance and Computed Tomography Imaging for Measurement of Primary Tumour Volume in Mesothelioma | Kevin Blyth, University of Glasgow, United Kingdom |
| MS13.05: TARGET TRIAL - A Randomised Controlled Trial to Compare the Diagnostic Yield of PET-CT TARGETed Pleural Biopsy Versus CT-guided Pleural Biopsy in Suspected Pleural Malignancy | Nick Maskell, University of Bristol, United Kingdom |
| MS13.06: Measurement Methods and Patient Outcomes in Malignant Pleural Mesothelioma | Manizha Kholmatov, University of Chicago, United States |
**Scientific Programme**

**Sunday, May 9, 2021**

*All times listed are in CEST (UTC +2) Time*

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Description</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MS13.07:</strong></td>
<td>Prognostic Significance of Loss of Skeletal Muscle in Patients with Malignant Pleural Mesothelioma</td>
<td>Andrew Kidd, St. John’s Hospital, United Kingdom</td>
</tr>
<tr>
<td></td>
<td>Receiving Chemotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>MS13.08:</strong></td>
<td>Texture Analysis for the Differentiation of Malignant Pleural Mesothelioma Histologic Subtypes on CT Scans</td>
<td>Eyjolfur Gudmundsson, UCL, United Kingdom</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Live Q&amp;A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>02:00 – 03:30</strong></td>
<td>Plenary IV: Immunotherapy - Checkpoint Blockade and Beyond</td>
<td>Chairs: Bruce Robinson, University of Western Australia, Australia</td>
</tr>
<tr>
<td></td>
<td>Track: Imaging, Immunology</td>
<td>Arnaud Scherpereel, Hospital of the Univ (CHU) of Lille, France</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PL04.01:</strong></td>
<td>Immunotherapy in Mesothelioma – Beyond Checkpoint Blockade</td>
<td>Joachim Aerts, Erasmus University Medical Center, Netherlands</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PL04.02:</strong></td>
<td>The Key Differences in the Immunologic Tumor Microenvironment in Mesothelioma vs Other Solid Cancers</td>
<td>Astero Klampatsa, Institute of Cancer Research, United Kingdom</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PL04.03:</strong></td>
<td>Imaging in Immunotherapy: Special Considerations and Potential Pitfalls</td>
<td>Sharyn Katz, Univ. of Pennsylvania Perelman School of Medicine, United States</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PL04.04:</strong></td>
<td>Mechanisms Underlying Checkpoint Inhibition Efficacy</td>
<td>Joost Lesterhuis, NCARD, Australia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PL04.05:</strong></td>
<td>Synergic Immunomodulating Antitumor Effect of IL-15 Superagonist and GITR Agonist After Local Non-ablative Hypofractionated Radiotherapy in Mesothelioma</td>
<td>Junichi Murakami, Latner Thoracic Surgery Research Laboratories, UHN, Canada</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PL04.06:</strong></td>
<td>Dynamic Changes in T Cell Receptor Diversity Correlate with Succesful Responses to Immune Checkpoint Blockade Outcomes in Murine Mesothelioma</td>
<td>Joel Kidman, NCARD, Australia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Live Q&amp;A</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Sunday, May 9, 2021

All times listed are in CEST (UTC +2) Time

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
</table>
| **12:30 – 13:00** | **SS02: Morning Session II**  
Track: N.A.  
Chairs: Sam Armato, The University of Chicago, United States  
Anna Nowak, NCARD, Australia |
| **SS02.01:** | The British Lung Foundation Mesothelioma Research Network  
John Moore-Gillon, St Bartholomew’s Hospital, London, United Kingdom |
| **SS02.02:** | European Thoracic Oncology Platform (ETOP)  
Paul Baas, The Netherlands Cancer Institute, Netherlands |
| **SS02.03:** | International Society for the Study of Pleura and Peritoneum (ISSPP)  
Robert Ramsay, Int'l Society for the Study of Pleura & Peritoneum, Australia |
| **SS02.04:** | Mesothelioma Applied Research Foundation (MARF)  
Mary Hesdorffer, Mesothelioma Applied Research Foundation, United States |
| **13:00 – 14:30** | **PL05: Plenary V: Cutting Edge 2020**  
Track: Clinical Trials, Radiation Oncology, Immunology  
Chairs: Raphael Bueno, Brigham And Women’s Hospital, United States  
Anna Nowak, NCARD, Australia |
| **PL05.01:** | CAR-T Cells: CAR T-Cell Therapy for Mesothelioma  
Prasad Adusumilli, Memorial Sloan Kettering Cancer Center, United States |
| **PL05.02:** | Immunotherapy and Radiotherapy in Mesothelioma  
Marc De Perrot, University Health Network (UHN), Canada |
| **PL05.03:** | State of the Art Genomics 2020  
Nicola Waddell, QIMR Berghofer, Australia |
| **PL05.04:** | Master Protocols for Salvage Therapy and the MIST Trial  
Dean Fennell, University of Leicester, United Kingdom |
| **PL05.05:** | A Safety Study of Avelumab plus SBRT in Malignant Mesothelioma  
Andreas Rimner, Memorial Sloan Kettering Cancer Ctr (MSKCC), United States |
| **PL05.06:** | 3D Mesothelioma Co-culture Models to Evaluate Innovative Anti-tumor Immunotherapies  
Nicolas Boisgerault, CRCINA - Inserm, France |
|            | **Live Q&A**                                                            |
### Sunday, May 9, 2021

**14:30 – 16:00**

**MS14: Plenary V: Cutting Edge 2020**  
**Track:** Clinical Trials, Radiation Oncology, Immunology  
Chairs: Raphael Bueno, Brigham And Women’s Hospital, United States  
Anna Nowak, NCARD, Australia

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Speaker</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS14.01</td>
<td>Synthetic Lethality and DNA Repair</td>
<td>Derek Richard</td>
<td>Queensland University of Technology, Australia</td>
</tr>
<tr>
<td>MS14.02</td>
<td>NF2</td>
<td>Yoshitaka Sekido</td>
<td>Aichi Cancer Center Research Institute, Japan</td>
</tr>
<tr>
<td>MS14.04</td>
<td>BAP1 Loss Predicts Therapeutic Vulnerability in Malignant Peritoneal Mesothelioma</td>
<td>Colin Collins</td>
<td>Vancouver Prostate Centre, Canada</td>
</tr>
<tr>
<td>MS14.05</td>
<td>Homologous Recombination Deficiency Mutagenesis During Early Evolution of Mesothelioma: Correlation with PARP Inhibitor Sensitivity</td>
<td>Aleksandra Bzura</td>
<td>University of Leicester, United Kingdom</td>
</tr>
<tr>
<td>MS14.06</td>
<td>Transglutaminase 2 Enhances Hepatocyte Growth Factor Signaling to Drive the Mesothelioma Cancer Cell Phenotype</td>
<td>Warren Naselsky</td>
<td>University of Maryland School of Medicine, United States</td>
</tr>
<tr>
<td>MS14.07</td>
<td>Tumor Treating Fields (TTFields) Reduce DNA Damage Repair Capacity in Malignant Pleural Mesothelioma, Leading to Effectiveness in Cellular and Animal Models</td>
<td>Moshe Giladi</td>
<td>Novocure, Israel</td>
</tr>
</tbody>
</table>

**Live Q&A**

### 14:30 – 16:00

**MS15: Parallel Mini-Symposia 15: Epidemiology and Asbestos Control**  
**Track:** Epidemiology and Asbestos Control, Mesothelioma Biology and Novel Targets  
Chairs: Peter Franklin, The University of Western Australia, Australia  
Ken Takahashi, Asbestos Diseases Research Institute, Australia

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Speaker</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS15.02</td>
<td>The Asian Mesothelioma Epidemic</td>
<td>Seong-Kyu Kang</td>
<td>Gachon University Gil Medical Center, South Korea</td>
</tr>
<tr>
<td>MS15.04</td>
<td>Malignant Mesothelioma in Australia: An Update from the Australian Mesothelioma Registry</td>
<td>Tim Driscoll</td>
<td>Sydney School of Public Health, Univ of Sydney, Australia</td>
</tr>
<tr>
<td>MS15.05</td>
<td>US Asbestos Control Methods: Historical Review of Prevention and Policy to Eliminate Exposure and Eradicate Asbestos-Related Diseases and the Future</td>
<td>Linda Reinstein</td>
<td>Asbestos Disease Awareness Org, United States</td>
</tr>
</tbody>
</table>
### SCIENTIFIC PROGRAMME

#### Sunday, May 9, 2021

All times listed are in CEST (UTC +2) Time

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:30 – 16:00</td>
<td><strong>MS16: Parallel Mini-Symposia 16: Biomarkers and Genetics II</strong>&lt;br&gt;<strong>Track</strong>: Biomarkers, Genetics/Bioinformatics, Mesothelioma Biology and Novel Targets&lt;br&gt;<strong>Chairs</strong>: Steven Mutsaers, Institute for Respiratory Health, Australia</td>
</tr>
<tr>
<td></td>
<td><strong>MS16.01</strong>: Fibulin-3 Is Not a Useful Diagnostic Biomarker in Malignant Pleural Mesothelioma: Final Results of the DIAPHRAGM Study&lt;br&gt;Selina Tsim, NHS Greater Glasgow &amp; Clyde, United Kingdom</td>
</tr>
<tr>
<td></td>
<td><strong>MS16.02</strong>: A New Chick Embryo Model to Aid in the Development of Personalised Therapies for Malignant Pleural Mesothelioma&lt;br&gt;Sarah Barnett, University of Liverpool, United Kingdom</td>
</tr>
<tr>
<td></td>
<td><strong>MS16.03</strong>: CDKN2A and MTAP Are Useful Biomarkers Detectable by Digital Droplet PCR to Identify Mesothelioma from Activated Mesothelial Phenotype&lt;br&gt;Yuen Yee Cheng, Asbestos Diseases Research Institute, Australia</td>
</tr>
<tr>
<td></td>
<td><strong>MS16.04</strong>: YAP1 Signaling Inhibitors Suppress the Mesothelioma Cancer Stem Cell Phenotype&lt;br&gt;Richard Eckert, Univ of Maryland School of Medicine, United States</td>
</tr>
<tr>
<td></td>
<td><strong>MS16.05</strong>: PPARα and PPARγ Activation Is Associated with Pleural Mesothelioma Invasion, but Therapeutic Inhibition Is Ineffective in Preclinical Models&lt;br&gt;Lizeth Orozco Morales, The University of Western Australia, Australia</td>
</tr>
<tr>
<td></td>
<td><strong>MS16.06</strong>: Both Long-Fibre Carbon Nanotubes and Asbestos Induce Sporadic Pleural Mesothelioma Recapitulating Human Disease: A Role for Epigenetic Mechanisms in Disease Development&lt;br&gt;Joaquin Zacarias Cabeza, University of Cambridge, United Kingdom</td>
</tr>
<tr>
<td></td>
<td><strong>MS16.07</strong>: In Vitro Volatomics to Pinpoint Mesothelioma-specific Biomarkers&lt;br&gt;Eline Janssens, University of Antwerp, Belgium</td>
</tr>
</tbody>
</table>

Live Q&A
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>00:30 – 02:00</td>
<td><strong>PL06: Plenary VI: Towards Tomorrow</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Track:</strong> Imaging, Surgery, Clinical Trials, Biomarkers, Genetics/Bioinformatics</td>
</tr>
<tr>
<td></td>
<td><strong>Chairs:</strong> Kenneth O’Byrne, QUT - Cancer &amp; Ageing Research Program, Australia</td>
</tr>
<tr>
<td></td>
<td>Andreas Rimner, Memorial Sloan Kettering Cancer Ctr (MSKCC), United States</td>
</tr>
<tr>
<td></td>
<td><strong>PL06.01:</strong> Flash Radiation for Mesothelioma</td>
</tr>
<tr>
<td></td>
<td>Keith Cengel, University of Pennsylvania, United States</td>
</tr>
<tr>
<td></td>
<td><strong>PL06.02:</strong> Using Bioinformatics to Find Novel Immunotherapy Combinations</td>
</tr>
<tr>
<td></td>
<td>Wee Loong (Melvin) Chin, NCARD, Australia</td>
</tr>
<tr>
<td></td>
<td><strong>PL06.03:</strong> Precision Imaging: Molecular Targets to Guide Therapy in Mesothelioma</td>
</tr>
<tr>
<td></td>
<td>Roslyn Francis, Univ of Western Australia/Sir Charles Gairdner Hosp., Australia</td>
</tr>
<tr>
<td></td>
<td><strong>PL06.04:</strong> MARS 3 and the Future of Surgery</td>
</tr>
<tr>
<td></td>
<td>David Waller, St Bartholomew’s Hospital, London, United Kingdom</td>
</tr>
<tr>
<td></td>
<td><strong>PL06.05:</strong> Biomarker Results from a Phase 2 Trial of Durvalumab with First Line Chemotherapy in Mesothelioma (DREAM)</td>
</tr>
<tr>
<td></td>
<td>Alistair Cook, NCARD, Australia</td>
</tr>
<tr>
<td></td>
<td><strong>PL06.06:</strong> Decoding Intra-tumoral Histologic Heterogeneity in Malignant Pleural Mesothelioma using Single-Cell Transcriptomics</td>
</tr>
<tr>
<td></td>
<td>David T Severson, Brigham and Women’s Hospital, United States</td>
</tr>
<tr>
<td></td>
<td><strong>Live Q&amp;A</strong></td>
</tr>
<tr>
<td>02:00 – 02:30</td>
<td><strong>Closing Session</strong></td>
</tr>
</tbody>
</table>
**Poster Listings**

**Track: Biomarkers, Genetics/Bioinformatics**

**P001:** Combined Deletion of Bap1, Nf2 and Cdkn2ab Causes Rapid Onset of Malignant Mesothelioma in Mice  
Jitendra Badhai, The Netherlands Cancer Institute, Netherlands

**P002:** In-Silico Analysis Reveals Novel Potential Molecular Targets Associated with MPM Patient’s Survival  
Luisa Bisceglia, University of Pisa, University of Siena, Italy

**P003:** Genes Differentially Expressed among Malignant Pleural Mesothelioma Histotypes  
Rossella Bruno, University Hospital of Pisa, Italy

**P004:** Hippo Imbalance Impacts on Chemotherapy Response of Malignant Pleural Mesothelioma Patients  
Rossella Bruno, University Hospital of Pisa, Italy

**P005:** Analysis of Efficacy of Chemotherapy According to Histology in Malignant Pleural Mesothelioma (MPM) Patients  
Susana Cedres, Vall D’hebron University Hospital and Institute of Oncology, Spain

**P006:** Rare, Non-BAP1-Related Potential Tumor Predisposition Gene Variants in Families with Mesothelioma and Other Cancers Identified Using Whole Genome Sequencing  
Mitchell Cheung, Fox Chase Cancer Center, United States

**P007:** Dynamic Gene Expression Changes Underpin Checkpoint Blockade Response in Murine Models of Mesothelioma and Renal Cell Cancer  
Wee Loong (Melvin) Chin, NCARD, Australia

**P008:** Exploring Alternative Methods of Detecting ENOX2 – a Biomarker for Mesothelioma  
Jenette Creaney, NCARD UWA, Australia

**P009:** National Centre for Asbestos Disease – Biobank  
Jenette Creaney, NCARD UWA, Australia

**P010:** Relationship Between Asbestos Exposure and Epigenetic Age Acceleration in Malignant Pleural Mesothelioma  
Giovanni Cugliari, Dept Of Medical Sciences, University of Turin, Italy

**P011:** Relationship Between Stochastic Epigenetic Mutations and Asbestos Exposure in Malignant Pleural Mesothelioma  
Giovanni Cugliari, Dept Of Medical Sciences, University of Turin, Italy

**P012:** The International Mesothelioma Program Database: Implementing a Relational Data Model to Support Collaborative Translational Research  
Mary Dao, Brigham and Women’s Hospital, United States

**P013:** Uptake and Efflux Transporter Polymorphisms Influence Cisplatin Treatment Outcome in Malignant Mesothelioma Patients  
Vita Dolžan, University of Ljubljana, Faculty of Medicine, Slovenia

**P014:** A Review of the Overlapping Genetic Mechanisms Between Ovarian Carcinomas and Malignant Mesothelioma  
Arianna Ferretti, Brown University, United States

**P015:** The Safety of Tumor Treating Fields (TTFields), An Anti-cancer Modality, When Delivered to the Torso of Healthy Rats  
Moshe Giladi, Novocure, Israel

**P016:** Transcription Landscape Analysis of Malignant Pleural Mesothelioma: A Retrospective Study  
Federica Grosso, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Italy

**P017:** Overview of Legal Rulings, Literature and Trials Involving Use of Genomic Information in Litigation Involving Causation of Mesotheliomas and Other Phenotypes  
Kirk Hartley, LSP Group - Law Science Policy, United States

**P018:** Exhaled Breath Analysis for Monitoring Therapeutic Response in Mesothelioma Patients Non-invasively  
Eline Janssens, University of Antwerp, Belgium
P019: Association Between microRNAs and Clinical, Inflammatory Factors in Patients with Malignant Pleural Mesothelioma Undergoing Multimodality Therapy
Michaela Kirschner, University Hospital Zurich, Switzerland

P020: The Role of Secretary Leukocyte Peptidase Inhibitor (SLPI) in Pleural Effusion for the Differential Diagnosis of Benign Asbestos Pleurisy from Pleural Mesothelioma and Other Effusions
Takumi Kishimoto, Research & Training Ctr for Asbestos-Related Diseases, Japan

P021: External Validation of a Breath Test for the Diagnosis of Malignant Pleural Mesothelioma: Results of an Interim Analysis
Kevin Lamote, Antwerp University, Belgium

P022: Headspace Analysis of Volatile Organic Compounds from Malignant Mesothelioma Cell Lines
Liam Little, Sheffield Hallam University, United Kingdom

P023: Novel MicroRNAs as Potential Biomarkers in Malignant Mesothelioma Patients from Hand-spinning Asbestos Exposure Area in Southeastern China
Jianlin Lou, Zhejiang Academy of Medical Sciences, China

P024: DNA Methylation Biomarker as Predictor of Survival in Patients with Malignant Pleural Mesothelioma
Giuseppe Matullo, University of Turin, Dept. Medical Sciences, Italy

P025: Untargeted Metabolomics Discovers Biomarkers in Serum Years Before Mesothelioma Diagnosis: The HUNT Study
Olav Toai Duc Nguyen, Norwegian University of Science & Technology, Norway

P026: Blood-based Prognostic Factors in Malignant Pleural Mesothelioma: A Retrospective Analysis
Isabelle Opitz, University Hospital Zurich, Switzerland

P027: Single Cell Sequencing Reveals Three Subpopulations of Mesothelioma Cells
Ann-Marie Patch, QIMR Berghofer Medical Research Institute, Australia

P028: Breath Analysis Allows Predicting Treatment Response in Malignant Pleural Mesothelioma Patients
Eline Schillebeeckx, University of Antwerp, Belgium

P029: Mutational Burden and Somatic Copy Number Alteration Profiles as Outcome Prediction Tools for Radial Surgery in Malignant Pleural Mesothelioma
Annabel Sharkey, Northern General Hospital, United Kingdom

P030: Exome-sequencing of Nine Brazilian Mesothelioma
Henrique Silveira, Barretos Cancer Hospital, Brazil

P031: The Single Nucleotide Polymorphism rs2235503 C>A Leads to Increased MSLN Gene Transcription and It Is Strongly Associated with the Levels of SMRP In Vivo
Roberto Silvestri, Università Di Pisa, Italy

P032: Implementation of a Novel Prospective Database for the Management of Clinicopathological Characteristics for Malignant Pleural Mesothelioma
Peter Tramontozzi, Brigham and Women’s Hospital, United States

P033: Biomarker Discovery Using Multiplex Analytical Techniques Can Improve the Diagnosis, Prognosis and Treatment Monitoring of Mesothelioma
Oana Voloaca, Sheffield Hallam University, United Kingdom

P034: Prognostic Value of Neutrophil-to-lymphocyte Ratio in Patients of Malignant Pleural Mesothelioma Treated with Nivolumab
Takashi Yokoi, Hyogo College of Medicine, Japan

P035: The Landscape of Copy Number Alterations Detected by Digital MLPA in Malignant Mesothelioma
Yoshie Yoshikawa, Hyogo College of Medicine, Japan

P036: Serum Calretinin as a Biomarker in Asbestos-Related Diseases
Cita Zupanc, University Medical Center Ljubljana, Slovenia
**Poster Listings**

**Track: Clinical Trials**

**P037:** Retrospective Evaluation of the Use of Pembrolizumab in Malignant Pleural Mesothelioma in a Real-World Australian Population
Tamkin Ahmadzada, The University of Sydney, Australia

**P038:** A Multicenter Randomized Phase III Trial of Dendritic Cells Loaded with Allogeneic Tumor Cell Lysate (MesoPher) in Mesothelioma Patients as Maintenance Therapy after Chemotherapy; Denim-trial
Robert Belderbos, Erasmus University Medical Center Rotterdam, Netherlands

**P039:** A Trial of Intra-Pleural Bacterial ImmunoTherapy in Malignant Pleural Mesothelioma (TILT) – A Randomised Feasibility Study Using the Trial Within a Cohort (TwiC) Methodology
Anna Bibby, Bristol Academic Respiratory Unit, United Kingdom

**P040:** Exploring the Barriers Faced by Mesothelioma Patients When Accessing Clinical Trials in the UK
Simon Bolton, Calderdale & Huddersfield NHS Foundation Trust, United Kingdom

**P041:** Gene Expression Analysis Results from a Phase 2 Trial of Durvalumab With First Line Chemotherapy in Mesothelioma (DREAM)
Alistair Cook, NCARD, Australia

**P042:** Real-life Data of Nivolumab in Patients with Recurrent Malignant Pleural Mesothelioma. Data from Expanded Access Program in Two Tertiary Cancer Centers in the Netherlands
Cornedine Jannette de Gooijer, Netherlands Cancer Institute, Netherlands

**P043:** PEMbrolizumab Plus Lenvatinib In Second Line and Third Line Malignant Pleural Mesothelioma Patients: A Single Arm Phase II Study (PEMMELA)
Cornedine Jannette de Gooijer, Netherlands Cancer Institute, Netherlands

**P044:** Phase II Study of Nivolumab and Ramucirumab for Patients with Previously Treated Mesothelioma: Hoosier Cancer Research Network LUN15-299
Arkadiusz Dudek, HealthPartners, United States

**P045:** Radiological Responses in the STELLAR Trial: Tumor Treating Fields plus Chemotherapy for First-line Malignant Pleural Mesothelioma (MPM)
Federica Grosso, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Italy

**P046:** TALAMESO: A Phase II Trial to Assess the Efficacy of Maintenance Treatment with Talazoparib Following First Line Platinum-based Chemotherapy in Pleural and Malignant Peritoneal Mesothelioma
Vahan Kepenekian, Lyon University Hospital, France

**P047:** Durvalumab with Chemotherapy as First Line Treatment in Advanced Pleural Mesothelioma - A Phase 3 Randomised Trial. The DREAM3R Trial
Isabelle Opitz, University Hospital Zurich, Switzerland

**P048:** Safety Outcomes of Intracavitary Cisplatin-fibrin Chemotherapy after Macroscopic Complete Resection for Malignant Pleural Mesothelioma: Insights from the Influencemeso Phase II Trial
Vahan Kepenekian, Lyon University Hospital, France

**P049:** The Mesotrap Trial – The Challenges of Recruiting a High Morbidity Subgroup of Malignant Pleural Mesothelioma Patients to an Interventional Study
Robert Rintoul, University of Cambridge, United Kingdom

**P050:** AMPLE-3: A Randomized Control Trial Comparing Combined Indwelling Pleural Catheter and Talc Pleurodesis with Video-Assisted Thorascopic Surgery for Management of Patients with Malignant Pleural Effusions
Calvinjit Sidhu, Sir Charles Gairdner Hospital, Australia

**P051:** A Phase 3, Open-Label, Randomized, Parallel Group Study to Evaluate the Efficacy and Safety of Adenovirus-Delivered Interferon Alpha-2b (rAd-IFN) in Patients with Malignant Pleural Mesothelioma
Daniel Sterman, NYU Langone Health, United States

**P052:** EORTC 1205: Randomized Phase 2 Study of Pleurectomy/Decortication (P/D) Preceded or Followed by Chemotherapy in Patients (pts) with Resectable Malignant Pleural Mesothelioma (MPM)
Jan Van Meerbeeck, Antwerp University Hospital, Belgium
## Track: Epidemiology and Asbestos Control

### P053: The Western Australia Mesothelioma Registry – Update
Fraser Brims, Curtin Medical School, Australia

### P054: Oxidative Stress and Inflammation in Automobile Mechanics Handling Asbestos Rich Vehicle Parts
Niraj Dhakal, Gandaki Medical College, Nepal

### P055: Gendered Experiences of Asbestos Exposure, Mesothelioma Risk and Pursuing a Civil Compensation Claim
Stephanie Ejegi-Memeh, School of Nursing and Midwifery, United Kingdom

### P056: An Audit to Explore the Demographics of Patients Diagnosed Within Kent
Louise Gilham, Meso UK / Kent Oncology Centre, United Kingdom

### P057: Does the Number of Patients with Mesothelioma Reported Through the Cancer Data Set Correlate with the Number of Patients Diagnosed Within Kent?
Louise Gilham, Meso UK / Kent Oncology Centre, United Kingdom

### P058: Burden of Asbestos Related Diseases in Taiwan based on Taiwan Cancer Registry and National Health Insurance databases
Lukas Lee, National Health Research Institutes, Taiwan

### P059: Prognostic Factors in Malignant Pleural Mesothelioma. Validation of the CALGB and EORTC Prognostic Systems
Jaroslaw Madrzak, Medical University of Gdańsk, Poland

### P060: Mesothelioma Outcomes in Manitoba 2001 – 2015
Andrew Maksymiuk, Cancercare Manitoba, Canada

### P061: Outcomes from Palliative Chemotherapy for Malignant Pleural Mesothelioma: The Impact of Platinum-pemetrexed
Abdullah Nasser, The Ottawa Hospital, Canada

### P062: Epithelioid Subtype Is the Most Significant Independent Favorable Prognostic Factor for Malignant Pleural Mesothelioma: A Real-world Danish Cohort
Vasiliki Panou, Odense University Hospital, Denmark

### P063: Human Ecology Associated with Asbestos-Related Diseases in Bangladesh
Md Shafiqu Rahman, Freelance, Bangladesh

### P064: Sex-differences and Gendered Experiences in Mesothelioma: Analysis of Asbestos Support Group Data in the England
Michaela Senek, University of Sheffield, United Kingdom

### P065: Three-decade Experience with Mesothelioma in an Academic Center
Paul Wheatley-Price, The Ottawa Hospital/University of Ottawa, Canada

## Track: Imaging

### P066: A Systematic Literature Review of Imaging Utilized for Diagnosis and Treatment of Malignant Peritoneal Mesothelioma
Bradley Carlson, Pritzker School of Medicine, United States

### P067: Computational Simulations to Determine the Safety and Efficacy of Tumor Treating Fields Delivered to the Lungs in Mesothelioma and NSCLC
Ze’ev Bomzon, Novocure, Israel

### P068: Novel Diagnosis Technique for Identification of Asbestos Fibres in Mesothelioma Samples Using LA-ICP-MS Imaging
Oana Voloaca, Sheffield Hallam University, United Kingdom

### P069: Ultrasound of the Chest in the Differential Diagnosis of Pleural Pathology and Mesothelioma
Turgun Yuldoshev, Tashkent Medical Academy, Uzbekistan
<table>
<thead>
<tr>
<th>#</th>
<th>Title</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>P070</td>
<td>Prediction of Response to ICI Treatment in Mesothelioma Using the eNose</td>
<td>Paul Baas, The Netherlands Cancer Institute, Netherlands</td>
</tr>
<tr>
<td>P071</td>
<td>Involvement of the M-CSF/IL-34/CSF-1R Pathway in Malignant Pleural Mesothelioma</td>
<td>Christophe Blanquart, CRCINA - INSERM UMR 1232, France</td>
</tr>
<tr>
<td>P072</td>
<td>Neo-antigen Vaccination and the Neo-antigen Response in Gemcitabine-treated Murine Mesothelioma</td>
<td>Jessica Boulter, National Centre for Asbestos Related Diseases, Australia</td>
</tr>
<tr>
<td>P073</td>
<td>Efficacy of Salvage Chemotherapy Following Treatment with Immune Checkpoint Inhibitors in Mesothelioma Patients</td>
<td>Luana Calabro, University Hospital of Siena, Italy</td>
</tr>
<tr>
<td>P074</td>
<td>Analysis of Efficacy of Immunotherapy According to Histology in Malignant Pleural Mesothelioma (MPM) Patients</td>
<td>Susana Cedres, Vall D´hebron University Hospital and Institute of Oncology, Spain</td>
</tr>
<tr>
<td>P075</td>
<td>Systematic Analysis of Chemo-immunotherapy Combinations That Lead to Durable Anti-tumour Responses in Murine Mesothelioma</td>
<td>Jonathan Chee, NCARD, Australia</td>
</tr>
<tr>
<td>P076</td>
<td>Harnessing the Synergy Between Radiotherapy and Immune Checkpoint Blockade in a Mouse Model of Mesothelioma</td>
<td>Synat Keam, NCARD, Australia</td>
</tr>
<tr>
<td>P077</td>
<td>Transient Depletion of Regulatory T Cells after Non-ablative Hypofractionated Radiation Boosts Abscopal Responses in Murine Malignant Mesothelioma</td>
<td>Mikihiro Kohno, University Health Network, Canada</td>
</tr>
<tr>
<td>P078</td>
<td>Oncolytic Viruses in Malignant Pleural Mesothelioma</td>
<td>Pamelbir Ladhar, Imperial College London, United Kingdom</td>
</tr>
<tr>
<td>P079</td>
<td>Nivolumab in a Patient with Malignant Pleural Mesothelioma Resulting in Persistently Elevated Troponin Levels Despite Clinical Remission of Myocarditis and Myositis: A Brief Report</td>
<td>Gabrielle Lie, Austin Health, Australia</td>
</tr>
<tr>
<td>P080</td>
<td>Combined Immune Checkpoint Blockade: In Vivo Validation of In Vitro Results</td>
<td>Elly Marcq, University of Antwerp, Belgium</td>
</tr>
<tr>
<td>P081</td>
<td>Identifying Prognostic Immune Biomarkers in Patients with Malignant Mesothelioma</td>
<td>Alison McDonnell, University of Western Australia, Australia</td>
</tr>
<tr>
<td>P082</td>
<td>Microfluidic Based Analysis of MPM-Tumor Infiltrating Lymphocytes Interaction</td>
<td>Stefania Oliveto, Ingm, Italy</td>
</tr>
<tr>
<td>P083</td>
<td>Does Immunoreactive Status of Neo-antigens Influence Their Ability to Induce Protection?</td>
<td>Alec Redwood, NCARD, Australia</td>
</tr>
<tr>
<td>P084</td>
<td>Evaluation of Host T Cell Responses to Genomically Predicted MM Neo-antigens</td>
<td>Alec Redwood, NCARD, Australia</td>
</tr>
<tr>
<td>P085</td>
<td>Monitoring Neo-antigen Responses Can Inform MM Therapy</td>
<td>Bruce Robinson, University of Western Australia, Australia</td>
</tr>
<tr>
<td>P086</td>
<td>Characterization of Immune Microenvironment in Primary Tumor and Tumor-involved Lymph Nodes from Patients with Malignant Pleural Mesothelioma: A Pilot Study</td>
<td>Daniel Sterman, NYU Langone Health, United States</td>
</tr>
<tr>
<td>P087</td>
<td>Salvage Ipilimumab and Nivolumab in Patients with Anti-PD-1-resistant Malignant Pleural Mesothelioma</td>
<td>Peter Szlosarek, Barts Cancer Institute, United Kingdom</td>
</tr>
<tr>
<td>P088</td>
<td>Contribution of Immunosuppressive Lymphocytes in Mesothelioma Cancer Development</td>
<td>Masahide Tone, Pacific Heart Lung and Blood Institution, United States</td>
</tr>
</tbody>
</table>
**POSTER LISTINGS**

<table>
<thead>
<tr>
<th>Poster</th>
<th>Title</th>
<th>Author(s)</th>
<th>Location(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P089</td>
<td>Circulating Biomarkers in Asbestos Exposure and Mesothelioma Before and After Radiation as Part of the SMARTER Protocol</td>
<td>Licun Wu, Toronto General Hospital, University Health Network, Canada</td>
<td></td>
</tr>
<tr>
<td>P090</td>
<td>Comparative Electron Microscope Asbestos Fiber Burden Analysis of Baby Powder in the Bottle and Body</td>
<td>Steven Kazan, Kazan, Mcclain, Satterley &amp; Greenwood, United States</td>
<td></td>
</tr>
<tr>
<td>P091</td>
<td>How to Not Find Asbestos Present in Cosmetic Talc in Order to Report “No Asbestos Found”</td>
<td>Steven Kazan, Kazan, Mcclain, Satterley &amp; Greenwood, United States</td>
<td></td>
</tr>
<tr>
<td>P092</td>
<td>Shipbreaking: Creating Accountability</td>
<td>Steven Kazan, Kazan, Mcclain, Satterley &amp; Greenwood, United States</td>
<td></td>
</tr>
<tr>
<td>P093</td>
<td>The Role of Company Doctors in Decisions About Public Health and Product Safety: A Cautionary Tale</td>
<td>Steven Kazan, Kazan, Mcclain, Satterley &amp; Greenwood, United States</td>
<td></td>
</tr>
<tr>
<td>P094</td>
<td>BAP1 Loss Is Associated with Higher ASS1 Expression in a Sub-Group of Epithelioid Mesothelioma Suggesting New Therapeutic Options</td>
<td>Sarah Barnett, University of Liverpool, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>P095</td>
<td>Identifying Genetic Profiles, Immunological Milieu and Cellular Characteristics Associated with Mesothelioma Susceptibility Using CC-MexTAg Mouse Model</td>
<td>Kiarash Behrouzfar, NCARD, Australia</td>
<td></td>
</tr>
<tr>
<td>P096</td>
<td>The Expression of Collagen Receptor uPARAP/Endo180 in Malignant Mesothelioma</td>
<td>Pinar Cakilkaya, Finsen Lab, Rigshospitalet/Biotech Research &amp; Innovation Ctr (BRIC), Denmark</td>
<td></td>
</tr>
<tr>
<td>P097</td>
<td>Heterozygous Germline BLM Mutations Increase Susceptibility to Asbestos and Mesothelioma</td>
<td>Michele Carbone, University of Hawaii Cancer Center, United States</td>
<td></td>
</tr>
<tr>
<td>P098</td>
<td>Overcoming Resistance to Arginine Deprivation Therapy in Malignant Pleural Mesothelioma</td>
<td>Josephine Carpentier, Barts Cancer Institute, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>P099</td>
<td>Butyrate Sensitizes Epithelioid Mesothelioma Cells to Oxaliplatin</td>
<td>Luis Vitetta, The University of Sydney and Medlab Clinical, Australia</td>
<td></td>
</tr>
<tr>
<td>P100</td>
<td>Immunomodulatory Activity of Epigenetic Drugs Combinations in Mesothelioma: Laying the Ground for New Immunotherapeutic Strategies</td>
<td>Alessia Covre, University Hospital of Siena, Italy</td>
<td></td>
</tr>
<tr>
<td>P101</td>
<td>Loss of a Single Copy of the Tumour Suppressor Gene NF2/Merlin Does Not Accelerate Pleural Disease Induced by Long-Fibre Carbon Nanotubes or Asbestos</td>
<td>Andrew Craxton, University of Cambridge, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>P102</td>
<td>Gemcitabine Elicits Enhanced T- and NK-cell-activation in Peripheral Blood of Malignant Mesothelioma Patients: Results from an Open Label Phase II Multicenter Trial (NVALT19)</td>
<td>Cornedine Jannette de Gooijer, Netherlands Cancer Institute, Netherlands</td>
<td></td>
</tr>
<tr>
<td>P103</td>
<td>Transglutaminase Serves as a Mesothelioma Cancer Stem Cell Survival Factor and Therapy Target</td>
<td>Richard Eckert, Univ of Maryland School of Medicine, United States</td>
<td></td>
</tr>
<tr>
<td>P104</td>
<td>Endogenous Retrovirus Expression Activates Type-I Interferon Signaling in an Experimental Mouse Model of Mesothelioma Development</td>
<td>Suna Sun, University of Zurich, Switzerland</td>
<td></td>
</tr>
<tr>
<td>P105</td>
<td>Contribution of RNA Editing to Mesothelioma Heterogeneity</td>
<td>Emanuela Felley-Bosco, University Hospital Zurich, Switzerland</td>
<td></td>
</tr>
</tbody>
</table>

**Track: Making the Case**

<table>
<thead>
<tr>
<th>Poster</th>
<th>Title</th>
<th>Author(s)</th>
<th>Location(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P089</td>
<td>Circulating Biomarkers in Asbestos Exposure and Mesothelioma Before and After Radiation as Part of the SMARTER Protocol</td>
<td>Licun Wu, Toronto General Hospital, University Health Network, Canada</td>
<td></td>
</tr>
<tr>
<td>P090</td>
<td>Comparative Electron Microscope Asbestos Fiber Burden Analysis of Baby Powder in the Bottle and Body</td>
<td>Steven Kazan, Kazan, Mcclain, Satterley &amp; Greenwood, United States</td>
<td></td>
</tr>
<tr>
<td>P091</td>
<td>How to Not Find Asbestos Present in Cosmetic Talc in Order to Report “No Asbestos Found”</td>
<td>Steven Kazan, Kazan, Mcclain, Satterley &amp; Greenwood, United States</td>
<td></td>
</tr>
<tr>
<td>P092</td>
<td>Shipbreaking: Creating Accountability</td>
<td>Steven Kazan, Kazan, Mcclain, Satterley &amp; Greenwood, United States</td>
<td></td>
</tr>
<tr>
<td>P093</td>
<td>The Role of Company Doctors in Decisions About Public Health and Product Safety: A Cautionary Tale</td>
<td>Steven Kazan, Kazan, Mcclain, Satterley &amp; Greenwood, United States</td>
<td></td>
</tr>
</tbody>
</table>

**Track: Mesothelioma Biology and Novel Targets**

<table>
<thead>
<tr>
<th>Poster</th>
<th>Title</th>
<th>Author(s)</th>
<th>Location(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P094</td>
<td>BAP1 Loss Is Associated with Higher ASS1 Expression in a Sub-Group of Epithelioid Mesothelioma Suggesting New Therapeutic Options</td>
<td>Sarah Barnett, University of Liverpool, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>P095</td>
<td>Identifying Genetic Profiles, Immunological Milieu and Cellular Characteristics Associated with Mesothelioma Susceptibility Using CC-MexTAg Mouse Model</td>
<td>Kiarash Behrouzfar, NCARD, Australia</td>
<td></td>
</tr>
<tr>
<td>P096</td>
<td>The Expression of Collagen Receptor uPARAP/Endo180 in Malignant Mesothelioma</td>
<td>Pinar Cakilkaya, Finsen Lab, Rigshospitalet/Biotech Research &amp; Innovation Ctr (BRIC), Denmark</td>
<td></td>
</tr>
<tr>
<td>P097</td>
<td>Heterozygous Germline BLM Mutations Increase Susceptibility to Asbestos and Mesothelioma</td>
<td>Michele Carbone, University of Hawaii Cancer Center, United States</td>
<td></td>
</tr>
<tr>
<td>P098</td>
<td>Overcoming Resistance to Arginine Deprivation Therapy in Malignant Pleural Mesothelioma</td>
<td>Josephine Carpentier, Barts Cancer Institute, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>P099</td>
<td>Butyrate Sensitizes Epithelioid Mesothelioma Cells to Oxaliplatin</td>
<td>Luis Vitetta, The University of Sydney and Medlab Clinical, Australia</td>
<td></td>
</tr>
<tr>
<td>P100</td>
<td>Immunomodulatory Activity of Epigenetic Drugs Combinations in Mesothelioma: Laying the Ground for New Immunotherapeutic Strategies</td>
<td>Alessia Covre, University Hospital of Siena, Italy</td>
<td></td>
</tr>
<tr>
<td>P101</td>
<td>Loss of a Single Copy of the Tumour Suppressor Gene NF2/Merlin Does Not Accelerate Pleural Disease Induced by Long-Fibre Carbon Nanotubes or Asbestos</td>
<td>Andrew Craxton, University of Cambridge, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>P102</td>
<td>Gemcitabine Elicits Enhanced T- and NK-cell-activation in Peripheral Blood of Malignant Mesothelioma Patients: Results from an Open Label Phase II Multicenter Trial (NVALT19)</td>
<td>Cornedine Jannette de Gooijer, Netherlands Cancer Institute, Netherlands</td>
<td></td>
</tr>
<tr>
<td>P103</td>
<td>Transglutaminase Serves as a Mesothelioma Cancer Stem Cell Survival Factor and Therapy Target</td>
<td>Richard Eckert, Univ of Maryland School of Medicine, United States</td>
<td></td>
</tr>
<tr>
<td>P104</td>
<td>Endogenous Retrovirus Expression Activates Type-I Interferon Signaling in an Experimental Mouse Model of Mesothelioma Development</td>
<td>Suna Sun, University of Zurich, Switzerland</td>
<td></td>
</tr>
<tr>
<td>P105</td>
<td>Contribution of RNA Editing to Mesothelioma Heterogeneity</td>
<td>Emanuela Felley-Bosco, University Hospital Zurich, Switzerland</td>
<td></td>
</tr>
</tbody>
</table>
P106: Results of the Meso-ORIGINS Feasibility Study and an Update on the PREDICT-Meso Accelerator Network
Katie Ferguson, Nhs Greater Glasgow & Clyde, United Kingdom

P107: Mouse Models of Mesothelioma: Unique Resources for Pre-clinical and Co-clinical Studies
Scott Fisher, The University of Western Australia, Australia

P108: Bioinformatic Analysis of Chromosomal Alterations in Malignant Pleural Mesothelioma
Sam Freyaldenhoven, Brigham and Women’s Hospital, United States

P109: Implication of CCL5-CCR5 Axis in Malignant Pleural Mesothelioma Chemoresistance
Laura Gerardelli, The Laboratory of Tumor and Development Biology, Univ of Liege, Belgium

P110: Antidepressants Targeting the Ubiquitin-proteasome-autophagy Pathway
Carlotta Giorgi, University Hospital Ferrara, Italy

P111: Selective Mesothelioma-Killing Ability of Novel Porphyrin-Based Photosensitisers in Photodynamic Therapy
Sarah Haywood-Small, Sheffield Hallam University, United Kingdom

P112: Inflammatory Cytokine Derived from Inflammasome in Tumor-associated Macrophages Enhances Malignant Potential of Malignant Pleural Mesothelioma
Daisuke Horio, Hyogo College of Medicine, Japan

P113: Exploring microRNA and Exosome Involvement in Drug Resistant Malignant Pleural Mesothelioma
Ben Johnson, Asbestos Diseases Research Institute, Australia

P114: Translation of Disulfiram, an Anti-alcoholism Drug as an Orphan Drug for Malignant Mesothelioma Treatment
Vinodh Kannappan, Disulfican Ltd, United Kingdom

P115: Malignant Mesothelioma with Loss of NF2: Are YAP and TAZ Rational Targets?
Aishwarya Kulkarni, Peter MacCallum Cancer Center, Australia

P116: Long-Fibre Carbon Nanotubes Induce a Higher Incidence of Malignant Pleural Mesothelioma in the MexTAG Transgenic Mouse Model, Replicating Asbestos-induced Mesothelioma
Marion MacFarlane, MRC Toxicology Unit, University of Cambridge, United Kingdom

P117: Homozygous Deletion of CDKN2A in Malignant Mesothelioma: Diagnostic Utility, Patient Characteristics and Survival in a UK Mesothelioma Centre
Kelly Marshall, NHS, United Kingdom

P118: Novel Over-expressed Genes in Malignant Pleural Mesothelioma Cells as Selected Targets for Innovative Therapies
Federica Morani, Università di Pisa-Dipartimento di Biologia, Italy

P119: Metabolic Profiling of Primary Mesothelioma Cell Lines to Elucidate a Network of Tumorigenic Processes
Michael Olanipekun, Imperial College London, United Kingdom

P120: Induction of Senescence or Apoptosis in BAP1 Wild Type Mesothelioma Cells in Response to EZH2 Inhibition: Role of CDKN2A
Giulia Pinton, University of Piemonte Orientale, Italy, Italy

P121: Targeting Thymidylate Synthase mRNA with a Novel Berberine Derivative in Malignant Mesothelioma
Carmen Plasencia, Applied Research Using Omic Sciences, Spain

P122: The Role of Mesothelioma-Associated Fibroblasts in Tumor Growth
Alexander Ries, Medical University of Vienna, Austria

P123: Developing a Novel Genetically Engineered Mouse Model of Malignant Pleural Mesothelioma
Claire Rooney, University of Glasgow, United Kingdom

P124: Impact of MET Amplification and Expression on Treatment Outcome in Malignant Mesothelioma
Eric Santoni-Rugiu, Dept. Pathology, Rigshospitalet, Copenhagen Univ. Hospital, Denmark
P125: YB-1 Is a Key Player in Aggressive Behaviour and Therapy Resistance in Mesothelioma
Karin Schelch, Medical University of Vienna, Austria

P126: Inactivation of p21-Activated Kinase 2 (Pak2) Inhibits the Development of Nf2-Deficient Malignant Mesothelioma
Eleonora Sementino, Fox Chase Cancer Center, United States

P127: Development of a Living Biobank of Patient-Derived Malignant Pleural Mesothelioma Organoid Models
Marie Shamseddin, Wellcome Sanger Institute, United Kingdom

P128: Simultaneous Inhibition of Both BCL-XL and MCL-1 Provides a Potent Therapeutic Strategy for Treating Malignant Pleural Mesothelioma
Xiao-Ming Sun, University of Cambridge, United Kingdom

P129: Loss of RIPK3 Expression Promotes Invasiveness of Malignant Pleural Mesothelioma Cells Via Activation of TGFβ Signaling
Yinfei Tan, Temple Fox Chase Cancer Center, United States

P130: Modulating the Local Tumour Microenvironment to Sensitise Mesothelioma to Chemotherapy
Caitlin Tilsed, NCARD, Australia

P131: BAP1 Inactivation Alters Cellular Migratory Behaviour Suggesting the ARP2/3 Complex as a Therapeutic Target in MPM
Martina Tripari, University of Liverpool, United Kingdom

P132: Defining and Targeting Tumor Associated Macrophages in Malignant Mesothelioma
Licun Wu, Toronto General Hospital, University Health Network, Canada

P133: Circulating Mesothelial Precursor Cells May Be a Novel Candidate for Screening and Prognosis in Malignant Pleural Mesothelioma
Licun Wu, Toronto General Hospital, University Health Network, Canada

P134: E-cadherin Is Down Regulated in MM and the Expression of E-cadherin Leads to MM Cell Resistance to FAK Inhibitor
Man Lee Yuen, Asbestos Diseases Research Institute, Australia

P135: STAT3 Inhibitor JSI-124 Induces Autophagic Cell Death in RN5 Murine Mesothelioma Cells
Chengke Zhang, The Second Hospital of Shandong University, China

Track: Mesothelioma in East Asia

P136: Malignant Pleural Mesothelioma of the Women in Our Hospital
Kohei Ando, Yokosuka Kyosai Hospital, Japan

Tianhui Chen, Zhejiang Cancer Hospital, China

P138: A Brisbane Mesothelioma Case with Worldwide Significance
Steven Kazan, Kazan, Mcclain, Satterley & Greenwood, United States

P139: Nivolumab for Malignant Mesothelioma: A Real-world Experience
Maiko Niki, Hyogo Collage of Medicine, Japan

Track: Nursing and Allied Health

P140: Non-NHS Funded Therapy vs Clinical Trials: The Importance of Patient Autonomy in Mesothelioma Treatment Decision Making
Simon Bolton, Calderdale & Huddersfield NHS Foundation Trust, United Kingdom

P141: Identifying the Severity of Psychosocial Symptoms among Patients Diagnosed with Mesothelioma. Do We Really Need Emotional Support Groups?
Arooj Fatima, Shaukat Khanum Cancer Hospital, Pakistan
Cheryl Routley, Asthma UK & British Lung Foundation Partnership, United Kingdom

P144: The Survival of a Mesothelioma Support Group through the Covid 19 Pandemic: Improvise and Overcome
Kate Slaven, Royal Papworth Hospital, United Kingdom

P145: Mesothelioma UK - Supporting Our Armed Forces. Raising Awareness and Providing Information and Support for Veterans/Armed Forces Personnel
Helen Wilkes, Mesothelioma UK/NHS, United Kingdom

P149: Correlation Between Reactive Fibrous Stroma in Diffuse Malignant Pleural Mesothelioma and Survival
Allen P. Burke, University of Maryland Medical Center, United States

P150: How Does the Histology of Pleural Mesothelioma Evolve Over Time?
Allen P. Burke, University of Maryland Medical Center, United States

P151: The Prevalence of Non-Mesothelial Neoplasm in Patient with Malignant Mesothelioma – A Retrospective Analysis of 484 Cases
Chin Keat Chan, Flinders University, Australia

P152: Analysis of Recurrence of Surgically Resected Malignant Pleural Mesothelioma
Joseph Friedberg, Univ of Maryland Medical Center, United States

P153: Guidelines for Pathological Diagnosis of Malignant Mesothelioma: 2021 Update
Aliya Husain, University of Chicago, United States

P154: Patterns of Distant Metastasis in Pleural Malignant Mesothelioma
Teklu Legesse, University of Maryland School of Medicine, United States

P155: BAP1 and MTAP in Cytology from Effusions Versus Biopsy in Malignant Mesothelioma Diagnosis; Equally Good?
Oluf Røe, Norwegian Univ of Science & Technology, Norway

P156: Tumor Vimentin Expression as a Prognostic Factor in Malignant Pleural Mesothelioma
Abdullah Nasser, The Ottawa Hospital, Canada

P157: Isolation of Cytotoxic Compounds Against Mesothelioma Cells from Epicoccum Nigrum, an Endophyte Isolated from Ferula Sumbul Plant
Irum Perveen, Quaid-i-Azam University, Pakistan

P158: Histological Analysis of Asbestos-exposed MexTAG Mice
Scott Fisher, The University of Western Australia, Australia

P159: Mesobank UK – A Globally Available Bioresource for Malignant Pleural Mesothelioma
Robert Rintoul, University of Cambridge, United Kingdom

P160: Expression of Glucocorticoid and Androgen Receptors in Malignant Mesothelioma (MM)
Jefree Schulte, The University of Wisconsin, United States
**Poster Listings**

**Track: Peritoneal Mesothelioma**

**P164:** Clarifying Diagnosis and Surgical Selection in 155 Patients with Peritoneal Mesothelioma; Early Oncologic Outcomes from a Monthly Video-conferencing National Multi-disciplinary Team Meeting  
Tom Cecil, PMI, United Kingdom

**P165:** Outcomes of Cytoreductive Surgery in Malignancy Peritoneal Mesothelioma: A Case Series  
Ye Ding, Princess Alexandra Hospital, Australia

**P166:** Retrospective Analysis of Efficacy and Safety of Cisplatin plus Pemetrexed for Treatment-naïve Malignant Peritoneal Mesothelioma  
Taiichiro Otsuki, Hyogo College of Medicine, Japan

**P167:** Achieving Equity in Treatment and Support for Peritoneal Mesothelioma: Establishing the UK National Peritoneal Mesothelioma Multi-disciplinary Team  
Samantha Westbrook, Hampshire Hospitals / Mesothelioma UK, United Kingdom

**Track: Surgery**

**P168:** Surgery combined with Hyperthermic IntraThoracic Chemotherapy (HITHOC) is associated with improved outcomes, compared to Surgery alone, in patients with Malignant Pleural Mesothelioma. Egyptian Experience  
Amr Al-Demery, National Cancer Institute, Cairo University, Egypt

**P169:** Pleurectomy/Decortication for Malignant Pleural Mesothelioma: A Single-Centre Experience  
Lawek Berzenji, Antwerp University Hospital, Belgium

**P170:** Diode-Pumped Laser for Lung-Sparing Surgical Treatment of Malignant Pleural Mesothelioma – Single-Surgeon Experience  
Servet Bölükbas, Evang. Kliniken Essen-Mitte, Essen, Germany, Germany

**P171:** Less-Invasive Approach for Macroscopic Complete Resection in Clinically Early Stage and Low-Volume Malignant Pleural Mesothelioma  
Servet Bölükbas, Evang. Kliniken Essen-Mitte, Essen, Germany, Germany

**P172:** Diaphragm and Phrenic Nerve Preservation During Lung-Sparing Surgery for Malignant Pleural Mesothelioma: The Impact on Patient Outcomes  
Melissa Culligan, Univ of Maryland Medical Center, United States

**P173:** Factors Influencing the Prognosis of Malignant Pleural Mesothelioma: A 5-year Analysis from a Tertiary Referral Centre  
Alan Dawson, University Hospitals of Leicester, United Kingdom

**P174:** The NCI-IASLC-MARF Joint Task Force System Captures Data That Has Potential to Standardize and Optimize Surgery-based Treatments for Malignant Pleural Mesothelioma  
Joseph Friedberg, Univ of Maryland Medical Center, United States

**P175:** Complications Associated with Extended Pleurectomy-Decortication Combined with Intraoperative Intrathoracic Povidone-Iodine Lavage for Malignant Pleural Mesothelioma  
Joseph Friedberg, Univ of Maryland Medical Center, United States

**P176:** Posterior Intercostal Lymph Nodes Are Highly Significant and Should Be Harvested During Any Therapeutic Operation for Malignant Pleural Mesothelioma  
Joseph Friedberg, Univ of Maryland Medical Center, United States
P177: Concordance in Lymph Node Pathology Obtained via Endobronchial Ultrasound Guided Transbronchial Needle Aspiration vs Surgical Resection in Patients with Malignant Pleural Mesothelioma
William Grier, University of Maryland Medical Center, United States

P178: Surgical Outcomes and Risk Factors in Curative-intent Surgery for Malignant Pleural Mesothelioma from Japanese Nationwide Annual Database
Masaki Hashimoto, Hyogo College of Medicine, Japan

P179: Incidence and Oncological Impact of Tumor Infiltration at Biopsy Site
Masaki Hashimoto, Hyogo College of Medicine, Japan

P180: Non-incisional Extended Pleurectomy–decortication for Left Side Malignant Pleural Mesothelioma
Yasuhiro Hida, Hokkaido University, Japan

P181: Experience of Lung-Sparing Pleurodectomy/Decortication with Intra-operation Adjuvant Therapy for Malignant Pleural Mesothelioma in a Single Center in Taiwan
Yei-San Hsieh, Taoyuan General Hospital, Taiwan

P182: Pleurectomy Decortication in the Treatment of Malignant Pleural Mesothelioma: Encouraging Results and Prognostic Implications Based on Experience with 355 Consecutive Patients
Moshe Lapidot, Brigham and Women’s Hospital, United States

P183: Prospective Validation of Our Multimodality Prognostic Score for Treatment Allocation of Malignant Pleural Mesothelioma Patients
Olivia Lauk, University Hospital Zuerich, Switzerland

P184: Analysis of Respiratory Function after P/D with Ventilation Scintigraphy
Toru Nakamichi, Hyogo College of Medicine, Japan

P185: Unusually Long Survival Rates for Epithelioid Mesothelioma Patients Observed with a Controversial Surgical Approach and Intraoperative Povidone-Iodine
Warren Naselsky, University of Maryland School of Medicine, United States

P186: The Results of Tri-modality Treatment with Extrapleural Pneumonectomy, Radiation, and Chemotherapy for Mediastinal Lymph Node Positive Malignant Pleural Mesothelioma
Kazunori Okabe, Bell Land General Hospital, Japan

P187: The Results of Trimodality Treatment with Extrapleural Pneumonectomy, Radiation, and Chemotherapy for Epithelioid Malignant Pleural Mesothelioma after 2011
Kazunori Okabe, Bell Land General Hospital, Japan

P188: Final Results of a Feasibility Trial Assessing Intrapleural Photodynamic Therapy Combined with Pleurectomy/Decortication Then Chemotherapy in Malignant Pleural Mesothelioma Patients
Arnaud Scherpereel, Hospital of the Univ (CHU) of Lille, France

P189: Outcome of 272 Consecutive Pleurectomies for Malignant Pleural Mesothelioma (MPM) 2005–2020: 5-Years Survival Rate 32% in R0-1 Resections
Jens Benn Sørensen, Rigshospitalet, Denmark

P190: Mesothelioma Patients’ Experiences of Follow-up Care Across Three National Health Service Hospital Trusts in the United Kingdom
Zoe Davey, Oxford Brookes University, United Kingdom

P191: Developing a Treatment Decision Support Tool for Managing Malignant Pleural Effusion in Patients Diagnosed with Mesothelioma
Arooj Fatima, Shaukat Khanum Cancer Hospital, Pakistan

P192: Management of Persistent Air Leaks Post Extended Pleurectomy and Decortication
William Grier, University of Maryland Medical Center, United States

P193: Management of Empyema Post Extended Pleurectomy and Decortication
William Grier, University of Maryland Medical Center, United States
**P194:** Intrapleural Liposomal Curcumin as a Palliative Treatment in Malignant Pleural Effusion: A Phase I Study Protocol Establishing Safety and Feasibility
Ash Hocking, Flinders University, Australia

**P195:** Examining the Role of Anamorelin in Mesothelioma (The ANTHEM Study): Rationale and Protocol
Siao Nge Hoon, Sir Charles Gairdner Hospital, Australia

**P196:** Impact of Symptoms and Physical Function on Quality of Life in Malignant Pleural Mesothelioma: Baseline Findings of an Ongoing Prospective Trial
Monica Malec, University of Chicago, United States

**P197:** Mesothelioma and Cough: An Exploration of the Literature
Kate Slaven, Royal Papworth Hospital, United Kingdom

**P198:** A Randomised Open-label Phase I/II Study Adding ONCOS-102 to Pemetrexed/Cisplatin in Patients with Unresectable Malignant Pleural Mesothelioma – 21 Month Analysis
Luis Paz-Ares, Hospital 12 Octubre, Spain
**iMig Wagner Medal**

The iMig Wagner Medal will be awarded during the closing session of the conference. In honor of the contributions of Dr. J. Christopher Wagner to the understanding of mesothelioma, its cause and goals for prevention, the International Mesothelioma Interest Group presents the Wagner Medal every two years to an individual who has made major original contributions to the understanding of mesothelioma, either in basic or applied research. The Wagner Medal is the highest honor presented by the International Mesothelioma Interest Group to a leader in the field.

- 2002 Marie-Claude Jaurand, PhD, France
- 2004 Bruce Robinson, MD, Australia
- 2006 Harvey Pass, MD, United States
- 2008 Brooke Mossman, PhD, United States
- 2010 Steven Albelda, MD, United States
- 2012 Joseph R. Testa, PhD, United States
- 2014 Raffit Hassan, MD, United States
- 2016 Courtney Broaddus, MD, United States
- 2018 Michele Carbone, MD, United States

**iMig Research Award**

The iMig Research Award will be awarded during the closing session of the conference. The iMig Research Award will be awarded every two years to recognize the potential significance and impact on the field of novel mesothelioma research (basic, translational or clinical) that has been published or presented since the prior International Meeting of the International Mesothelioma Interest Group. Research to be presented during the current Conference would make an investigator eligible for nomination for the iMig Research Award.

**iMig Advancement Award**

The iMig Advancement Award will be awarded during the closing session of the conference. The iMig Advancement Award may be awarded every two years to an individual who has made significant and sustained contributions of service to the mission of the International Mesothelioma Interest Group and the mesothelioma community.

**Developing Nations Award**

The Developing Nations Awards will be presented during the closing session of the conference.

- **Niraj Dhakal**, Nepal  
  P054: Oxidative Stress and Inflammation in Automobile Mechanics Handling Asbestos Rich Vehicle Parts

- **Arooj Fatima**, Pakistan  
  P141: Identifying the Severity of Psychosocial Symptoms Among Patients Diagnosed with Mesothelioma. Do We Really Need Emotional Support Groups?

- **Irum Perveen**, Pakistan  
  P191: Developing a Treatment Decision Support Tool for Managing Malignant Pleural Effusion in Patients Diagnosed with Mesothelioma

- **Shafiqur Rahman**, Bangladesh  
  P063: Human Ecology Associated with Asbestos-Related Diseases in Bangladesh
Young Investigator Award recipients will receive their awards during the closing session of the conference.

Tamkin Ahmadzada, Australia
MS11.06: Extracellular Vesicles as Novel Biomarkers in Malignant Pleural Mesothelioma
P037: Retrospective Evaluation of the Use of Pembrolizumab in Malignant Pleural Mesothelioma in a Real World Australian Population

Surein Arulananda, Australia
MS14.03: Malignant Pleural Mesothelioma Is an Exquisite Target for BCL-XL Inhibitors Due to Its Dependency on the BCL-XL Pro-survival Protein

Sarah Barnett, United Kingdom
MS16.02: A New Chick Embryo Model to Aid in the Development of Personalised Therapies for Malignant Pleural Mesothelioma
P094: BAP1 Loss is Associated with Higher ASS1 Expression in a Sub-Group of Epithelioid Mesothelioma Suggesting New Therapeutic Options

Cornedine Jannette de Gooijer, Netherlands
PL02.03: Switch Maintenance Gemcitabine after First Line Chemotherapy in Patients with Malignant Mesothelioma; Updated Results of a Multicenter Open Label Phase II Trial (NVALT19)
MS07.07: Optimizing Survival Prediction in Malignant Mesothelioma; Development and External Validation of a Clinical Prediction Model (MESOPRO)
P042: Real-life Data of Nivolumab in Patients with Recurrent Malignant Pleural Mesothelioma. Data from Expanded Access Program in Two Tertiary Cancer Centers in the Netherlands

P043: PEMbrolizumab Plus Lenvatinib In Second Line and Third Line Malignant Pleural Mesothelioma Patients: A Single Arm Phase II Study (PEMMELA)
P102: Gemcitabine Elicits Enhanced T- and NK-cell-activation in Peripheral Blood of Malignant Mesothelioma Patients: Results from an Open Label Phase II Multicenter Trial (NVALT19)

Lise Mangiante, France
MS11.05: MESOMICS Project: Deep Genomic Characterisation and Integration Unveil Specific Cancer Tasks and Evolutionary Traits, Together with Specific Morphological and Molecular Profiles with Important Clinical Implications

Warren Naselsky, United States
MS14.06: Transglutaminase 2 Enhances Hepatocyte Growth Factor Signaling to Drive the Mesothelioma Cancer Cell Phenotype
P185: Unusually Long Survival Rates for Epithelioid Mesothelioma Patients Observed with a Controversial Surgical Approach and Intraoperative Povidone-Iodine

Michael Offin, United States
MS09.06: Molecular Characterization of Peritoneal Mesotheliomas

Selina Tsim, United Kingdom
MS16.01: Fibulin-3 Is Not a Useful Diagnostic Biomarker in Malignant Pleural Mesothelioma: Final Results of the DIAPHRAGM Study

Benjamin Wadowski, United States
MS08.05: High PD-L1 (CD274) RNA Expression is Associated with Diverse Transcriptional Phenotypes in Malignant Pleural Mesothelioma

Wesley Wilson, Canada
MS03.04: Where There’s a TIL, There’s a Ray: Image Guided X-rays Induce Changes in T-cell Phenotypes in Mesothelioma Tumour Micro-environments
EXHIBITION INFORMATION
**Exhibition Details**

During the meeting, attendees can interact with the Virtual Exhibitors. They can view any information such as videos, download brochures, access social media, request a one-on-one conversation, or send exhibits staff a direct message.

---

**Asbestos Disease Awareness Organization (ADAO)**

The Asbestos Disease Awareness Organization (ADAO) is the largest independent nonprofit in the U.S. dedicated to preventing asbestos exposure to eliminate mesothelioma, lung cancer, and all other asbestos-related diseases through education, advocacy and community initiatives. Annually, nearly 40,000 Americans die from preventable asbestos-caused diseases.

[www.adao.us](http://www.adao.us)

---

**Asbestos Safety and Eradication Agency**

The Asbestos Safety and Eradication Agency is a Commonwealth statutory agency. We were established in 2013 to administer the National Strategic Plan for Asbestos Awareness and Management. Our aim is to prevent exposure to asbestos fibres in order to eliminate asbestos-related diseases in Australia by coordinating the implementation of the National Strategic Plan. We oversee national actions to improve asbestos awareness and the effective and safe management, removal and disposal of asbestos. To do this we work collaboratively with a variety of stakeholders – including state and territory governments, local government, employer bodies, employee representatives and the non-government and corporate sectors.

---

**Asbestos Diseases Society of Australia Inc. (ADSA)**

ADSA is Australia’s leading health and advocacy association assisting persons affected by mesothelioma - asbestosis - silicosis - lung cancer. The organisation has played a crucial role in helping Australians affected by asbestos-related diseases since 1979. Our Purpose is to save lives, and Our Values underpin all that we do:

**JUSTICE** - To ensure access to fair and just compensation
Asbestos.com at The Mesothelioma Center

The Medical Outreach Department at The Mesothelioma Center provides free informational resources and financial assistance for patients with asbestos-related diseases. We help patients with asbestos-related lung cancer, as well as patients with pleural or peritoneal mesothelioma, to access resources and authentic economic aid to those affected by asbestos or mesothelioma. In addition, the Medical Outreach team helps guide patients to secure travel grants, connect with experts, and work with healthcare professionals to eliminate barriers to care. For patients exploring possible legal options, the Medical Outreach team explains the process, rights, and other important factors to help ensure best possible outcomes.

Bristol-Myers Squibb

Bristol-Myers Squibb is a leading global biopharma company focused on discovering, developing and delivering innovative medicines for patients with serious diseases in areas including oncology, hematology, immunology, cardiovascular and neuroscience. Our employees work every day to transform patients’ lives through science.

www.bms.com

Canadian Mesothelioma Foundation

The Canadian Mesothelioma Foundation is a registered charity founded by people personally affected by mesothelioma. We raise awareness about the link between mesothelioma and asbestos, and support those affected by mesothelioma. We also provide grants to mesothelioma programs and are currently developing a network of expertise in diagnosis and treatment across Canada.

www.cmfonline.org

International Thoracic Oncology Nurses Forum (ITONF)

The International Thoracic Oncology Nurses Forum (ITONF) is a global group of thoracic oncology nurses operating since 2009. ITONF works tirelessly to promote improvements in nursing care for patient benefit within the fast-changing landscape of thoracic oncology nursing.

www.itonf.com
Kazan Law
Since 1974, Kazan Law has been dedicated to representing mesothelioma victims. We have been winning jury and court trials, getting precedent-setting rulings that make California asbestos law, and obtaining justice for our clients. Kazan Law was recognized by The Wall Street Journal as America’s most important asbestos bankruptcy trust lawyers.
www.kazanlaw.com

Leigh Day
Leigh Day Lawyers
Our team has a formidable reputation in asbestos litigation as a consequence of representing victims for over 30 years in the UK and abroad. Our clients keep 100% of their compensation. Our team has achieved the highest compensation awards for pain, suffering and care for mesothelioma victims. We have protected the rights of victims of asbestos related diseases through Judicial Review and Supreme Court cases whilst representing the Asbestos Victims Support Group Forum UK. Read about some of them on our website. Our lawyers raise funds for asbestos charities throughout the UK. We deal with cases quickly and aim to obtain compensation for our clients within 3-6 months.
www.leighday.co.uk/our-services/asbestos-and-industrial-diseases

Novocure Medical Affairs
Novocure is a global oncology company working to extend survival in some of the most aggressive forms of cancer through the development of its innovative therapy, Tumor Treating Fields (TTFields). Novocure has ongoing clinical trials investigating TTFields in studies targeting specific lung, pancreatic, ovarian, hepatic, and gastric cancers, brain metastasis, and glioblastoma.

National Centre for Asbestos Related Diseases (NCARD)
The National Centre for Asbestos Related Diseases (NCARD) is based at the University of Western Australia in Perth. More than 30 research staff and students focus on mesothelioma research.

Roche
Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people’s lives. The combined strengths of pharmaceuticals and diagnostics have made Roche the leader in personalised healthcare – a strategy that aims to boldly transform and personalise healthcare to prevent, diagnose and treat each and every patient more effectively, while creating a more sustainable healthcare ecosystem.
www.roche-australia.com
**PL01.04: Spatial Intra-Tumor Molecular Heterogeneity in Malignant Pleural Mesothelioma**

Meiller C1, Montagne F2, Hirsch T1, Caruso S1, de Wolf J3, Bayard Q1, Assié J4, Meunier L1, Blum Y4, Quetel L1, Gibault L5, Pintilie E2, Badoual C5, Copin M6, Letouzé E1, Scherpereel A2, Zucman-Rossi J1, Le Pimpec-Barthes F6, Jaurand M1, Jean D1

1Inserm - Centre de Recherche des Cordeliers, Paris, France, 2CHRU de Lille, Lille, France, 3Hôpital Foch, Paris, France, 4Ligue contre le Cancer, Paris, France, 5HEGP - APHP, Paris, France, 6CHU Angers, Angers, France

Objectives: Malignant pleural mesothelioma (MPM) is a heterogeneous cancer characterized by a diffuse locoregional growth within the thoracic cavity. Better knowledge of molecular and cellular intra-tumor heterogeneity throughout the thoracic cavity is required to develop efficient therapies.

Methods: Intra-tumor heterogeneity was investigated in 16 patients biopsied at distinct anatomic sites (apex, side wall, costo-diaphragmatic and highly metabolic site detected by PET scan when present). Paired biopsies and five derived primary cell lines were screened by targeted sequencing. Part of the cohort was also deeply characterized by whole exome sequencing, RNA-seq and DNA methylation profiling. Molecular classification and recently defined histo-molecular gradients were assessed, as were the cell populations infiltration of the tumor microenvironment.

Results: Sequencing analysis showed that most of the protein-altering somatic variants were common between paired samples from a given patient. However, we identified heterogeneous variants notably in NF2, the well-known mesothelioma driver tumor suppressor gene. Furthermore, we highlighted subclonal tumor populations shared among paired biopsies, suggesting a polyclonal dissemination of the tumor. Chromosomal abnormalities profiles were similar between different regions within the same tumor suggesting that the main chromosomal alterations occurring in MPM are early events of mesothelial carcinogenesis. Transcriptomic analysis showed major differential gene expression between anatomic sites, leading to the dysregulation of specific pathways notably linked to cell adhesion and extracellular matrix. Accordingly, histo-molecular gradient determining the proportions of epithelioid-like and sarcomatoid-like cellular entities varied between these samples. These changes were linked to epigenetic mechanisms in two patients. Finally, we found substantial spatial intra-tumor heterogeneity of the immune microenvironment with differential expression of immune mediators and immune checkpoints, and differential infiltration of immune populations. These changes led to a switch from a hot to a cold immune profile in three patients.

Conclusion: This study is the first to report on the multi-omics profiling of a substantial series of multi-site MPM tumor samples. Spatial intra-tumor heterogeneity is complex in MPM and varies among patients. We highlighted multiple types of heterogeneity, i.e. (i) genetic, (ii) transcriptomic, (iii) epigenetic and (iv) in the immune landscape of the tumor microenvironment. These results support the need for multi-sampling for the implementation of molecular-based precision medicine in MPM.

Intra-tumor heterogeneity; tumor microenvironment; clonal evolution

**PL01.05: The MexTAg Collaborative Cross: Identifying the Genetic Basis of Mesothelioma. An Interim Report**

Fisher S1,2, Burton K1,2, Lesterhuis W2,6, Bueno R3, Morahan G1, Young S4, Nowak A2,3, Lake R1,2

1School of Biomedical Sciences. The University of Western Australia, Perth, Australia, 2National Centre for Asbestos Related Diseases (NCARD), Perth, Australia, 3School of Medicine. The University of Western Australia, Perth, Australia, 4Centre for Diabetes Research. Harry Perkins Institute of Medical Research, Perth, Australia, 5Division of Thoracic Surgery. Brigham and Women’s Hospital, Boston, USA, 6Telethon Kids Institute, Perth, Australia

Objectives: This study combines two innovative mouse models for the first time in a major gene discovery project, and integrates them with two clinical genomic datasets to identify key pathways that act to promote, or protect against mesothelioma following asbestos exposure.
Mesothelioma development after asbestos exposure is highly variable: some people do not develop disease despite high level exposure for many years, while others get disease with no known history of contact. There is good evidence that at least part of the difference in susceptibility to mesothelioma is genetic, but the genes involved remain mostly unknown. Conventional genetic studies have attempted to identify mesothelioma susceptibility genes, but these studies are problematic because detection of significant associations is compromised by the genetic heterogeneity of study populations and by other environmental complications (the type and amount of carcinogen exposure, smoking and diet) between cases, and between cases and control groups. The genes detected by conventional genetic studies have a minor impact on disease risk and it is not known where in the disease pathway they act, nor how they contribute to disease mechanisms.

Here we report on our study designed to rapidly identify genes associated with mesothelioma susceptibility and resistance by combining the Collaborative Cross (CC) with our well-characterised MexTAg mesothelioma mouse model. The CC is a powerful mouse resource specifically developed to rapidly identify genes associated with complex traits, while MexTAg mice rapidly, uniformly and predictably develop mesothelioma, but only after asbestos exposure.

**Methods:**

**Aim 1:** Generate CC-MexTAg mice and expose to asbestos. The CC is a collection of recombinant inbred mouse lines covering over 90% of the common allelic diversity of the mouse species. The genome sequences of each of the CC lines are known. Each CC line will be crossed with MexTAg mice and the resulting CC-MexTAg progeny exposed to asbestos. Exposed mice will be monitored for various phenotypes including; overall survival, the time to disease onset (latency) and the time to disease progression.

**Aim 2:** Identify candidate modifier genes. Using our established informatics pipeline, we can rapidly identify alleles that 1) protect mice against, or sensitise to mesothelioma, and 2) influence the pathology and course of the disease.

**Aim 3:** Identify human orthologs and interrogate human mesothelioma datasets. We will identify human orthologs of candidate modifier genes and their respective biological pathways associated with asbestos induced carcinogenesis in human mesothelioma datasets.

**Results:** We have generated 50+ unique CC MexTAg lines and exposed their progeny to asbestos. We observed considerable variation in overall survival and disease latency, but not disease progression; demonstrating that host genetic factors affect asbestos related disease (ARD), but play little role in moderating established disease. Identification of numerous quantitative trait loci (QTL) across different phenotypes suggests interaction of multiple modifier genes are associated with ARD following asbestos exposure.

**Conclusion:** Our data indicate that host genetic factors can affect susceptibility to asbestos associated disease. Validation of candidate modifier genes and their respective biological pathways associated with asbestos induced carcinogenesis in human mesothelioma datasets continues.

**Keywords:** mesothelioma, MexTAg, collaborative cross, host genetics, genetic modifiers of disease

---

**PL01.06: Multiple Cancers in 416 Patients with Malignant Mesothelioma**

Panou V1,2, Hansen J4, Meristoudis C2, Røe O3,5,6

1Odense University Hospital, Odense, Denmark, 2Aalborg University Hospital, Aalborg, Denmark, 3Aalborg University, Aalborg, Denmark, 4Danish Cancer Society, Copenhagen, Denmark, 5Levanger Hospital, Levanger, Norway, 6Department of Cancer Research and Molecular Medicine Norwegian University of Science and Technology (NTNU), Trondheim, Norway

**Plenary I: Origins of Mesothelioma, Virtual, May 7, 2021, 1:00 PM - 2:30 PM**

**Objectives:** We aimed to investigate the manifestation of other cancers in patients with malignant mesothelioma (MM).

**Methods:** The study population comprises patients diagnosed with pleural (MPM) or peritoneal MM during 1972-2015 at the North Denmark Region (NDR). Two pathologists re-evaluated all cases to verify the diagnosis. The patients’ history of malignancy, asbestos exposure, clinical and pathological information was acquired through nationwide Danish Registries and the individual medical journals. Fisher’s exact and Student’s t-test were used for statistical analyses. The crude incidence cancer rate for the
population of the NDR was determined through NORDCAN (http://www-dep.iarc.fr/NORDCAN/English/frame.asp).

**Results:** Of 416 included patients, 47 had been diagnosed with one and three patients with two previous malignancies (Figure 1). Multiple cancer primaries correlated significantly with older age at MM diagnosis ($p=0.01$) and non-epithelioid subtype ($p=0.04$). The most frequent neoplasm was prostate cancer ($N=14$, 28%, Figure 1). Hodgkin lymphoma was over-represented, while lung and gastric cancer were under-represented in the MM population (Table 1). One of the two patients with Hodgkin lymphoma never received thoracic radiation, a suggested risk factor for MPM, and developed MPM at 69. The other patient received thoracic radio-treatment and developed MPM at 56. Both were occupationally exposed to asbestos.

**Conclusion:** The lacking over-representation of malignancies suggests the absence of typical genetic syndromes, except from Hodgkin lymphoma. Common etiological factors might influence the genesis of the latter and MPM. The under-representation of lung and gastric cancer may be due to the patients’ low survival rate, not reaching the age of MM manifestation. The association of multiple malignant diagnoses with the more aggressive non-epithelioid subtype and older age at diagnosis has not been reported before. The former indicates that pleural effusion cytology is of limited value for this patient group, as it cannot diagnose the sarcomatoid component, while both findings warrant further investigation.

**Keywords:** multiple cancers, mesothelioma, Hodgkin lymphoma, lung cancer, gastric cancer
PL01.07: Asbestos Induces Mesothelial Cell Transformation via HMGB1-Driven Autophagy

Xue J1,2, Paterniani S3, Giorgi C3, Suarez J1, Goto K4, Bononi A1, Tanji M3, Novelli F1, Pastorino S1, Xu R1, Caroccia N3, Dogan U5, Pass H6, Tognon M3, Pinton P3, Gaudino G1, Mak T7, Carbone M1, Yang H1

1University of Hawai’i Cancer Center, Honolulu, United States, 2University of Hawai’i, John A. Burns School of Medicine, Honolulu, United States, 3University of Ferrara, Dept of Medical Sciences, Laboratory for Technologies of Advanced Therapies, Ferrara, Italy, 4Hirosima University, Dept of Urology, Inst of Biomedical & Health Sciences, Hiroshima, Japan, 5University of Iowa, Chemical & Biochemical Engineering & Center for Global & Regional Environmental Research, Iowa City, United States, 6New York University Langone Medical Center, Dept of Cardiothoracic Surgery, New York, United States, 7The Campbell Family Inst for Breast Cancer Res, Princess Margaret Cancer Center, University of Health Network, Toronto, Ontario, Canada

Plenary I: Origins of Mesothelioma, Virtual, May 7, 2021, 1:00 PM - 2:30 PM

Asbestos causes malignant transformation of primary human mesothelial cells (HM), leading to mesothelioma. The mechanisms of asbestos carcinogenesis remain enigmatic, as exposure to asbestos induces HM death. However, some asbestos-exposed HM escape cell death, accumulate DNA damage and may become transformed. We previously demonstrated that upon asbestos exposure HM and reactive macrophages released the high mobility group box 1 (HMGB1) protein that becomes detectable in the tissues nearby asbestos deposits where HMGB1 triggers chronic inflammation. HMGB1 is also detectable in the sera of asbestos-exposed individuals and mice. Searching for additional biomarkers, we found higher levels of the autophagy marker ATG5 in sera from asbestos-exposed individuals compared to unexposed controls. As we investigated the mechanisms underlying this finding, we discovered that the release of HMGB1 upon asbestos exposure promoted autophagy, allowing a higher fraction of HM to survive asbestos exposure. HMGB1 silencing inhibited autophagy and increased asbestos-induced HM death, therefore decreasing asbestos-induced HM transformation. We demonstrated that autophagy was induced by the cytoplasmic and extracellular fractions of HMGB1 via the engagement of the RAGE receptor and Beclin 1 pathway, while nuclear HMGB1 did not participate in this process. We validated our findings in a novel unique mesothelial conditional HMGB1-knockout (HMGB1-cKO) mouse model. Compared to HMGB1 wild-type mice, mesothelial cells from HMGB1-cKO mice showed significantly reduced autophagy and increased cell death. Autophagy inhibitors chloroquine (CQ) and desmethylclomipramine (DCMI) increased cell death and reduced asbestos-driven foci formation. In summary, HMGB1 released upon asbestos exposure induces autophagy, promoting HM survival and malignant transformation.

Millions of people have been exposed to asbestos and are at increased risk of developing mesothelioma, an aggressive malignancy resistant to current therapies. Here, we elucidated critical steps in asbestos carcinogenesis: asbestos induced the release of HMGB1 that triggered autophagy. Autophagy activation constituted a key biological process that allowed some mesothelial cells to survive asbestos cytotoxicity and consequently increased the fraction of DNA-damaged HM susceptible to malignant transformation. We found that the inhibition of autophagy using either chloroquine (CQ) or the anti-depressant drug, desmethyldclomipramine (DCMI), increased asbestos-induced cell death and reduced asbestos-mediated cell transformation. Our data suggest that these FDA-approved drugs might be repurposed to protect high-risk asbestos-exposed individuals from developing mesothelioma.

HMGB1, autophagy, cell death, asbestos, mesothelioma

MS01.03: Differential Diagnosis of Biphasic Malignant Pleural Mesothelioma on Pleural Effusions by Gene Expression

Bruno R1, Ali G1, Poma A2, Proietti A1, Libener R3, Roveta A4, Maconi A4, Grosso F5, Ribeichini A6, Chella A7, Fontanini G2

1Unit of Pathological Anatomy, University Hospital of Pisa, Pisa, Italy, 2Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy, 3Pathology Unit, SS Antonio and Biagio General Hospital, Alessandria, Italy, 4Infrastruttura Ricerca, Formazione e Innovazione, SS Antonio and Biagio General Hospital, Alessandria, Italy, 5Mesothelioma Unit, SS Antonio and Biagio General Hospital, Alessandria, Italy, 6Endoscopic Section of Pneumology, University Hospital of Pisa, Pisa, Italy, 7Unit of Pneumology, University Hospital of Pisa, Pisa, Italy
Parallel Mini-Symposia 01: Pathology, Virtual, 
May 7, 2021, 2:30 PM - 4:00 PM

Objectives: Pleural effusions are the first and sometimes only available diagnostic material for malignant pleural mesothelioma (MPM) patients. However, MPM diagnosis on pleural effusions is rarely conclusive since some cytological features are shared by malignant and benign lesions. We have previously developed a 117-gene expression panel able to discriminate epithelioid (E) MPM from reactive mesothelial hyperplasia (MH) directly on pleural effusions. The aim of this study is to test the same panel in the differential diagnosis of biphasic (B) MPM pleural effusions. Indeed, B-MPM has a greater heterogeneity than E-MPM, sharing both epithelioid and sarcomatoid components, and constitutes the second most common MPM histotype.

Methods: We have previously developed a classification model based on the expression profile of 117 genes, analyzed by the NanoString System, using as training set 34 E-MPM and 20 MH tissues; on an independent test set of pleural effusions (23 E-MPM and 11 MH) a diagnostic accuracy of 96% was then achieved.

Herein, we extended the analysis to pleural effusions from 9 B-MPM patients (smears and cell-blocks) with a histological confirmation of diagnosis.

First, the overlap of the expression patterns of E and B-MPM effusions was evaluated by principal component analysis (PCA). Then, we used the previously identified classification model to classify samples as malignant or benign.

This research was funded by The Kazan McClain Partners’ Foundation.

Results: PCA showed an evident overlap between the E-MPM and B-MPM expression profiles as expected since malignant cells from the sarcomatoid component do not shed into the effusions (Figure 1).

Our classification model correctly classified as malignant 7 out of 9 B-MPM (77.8%) independently of the percentage of sarcomatoid component determined on paired histological samples and ranging from 15 to 70%.

Conclusion: Although preliminary, our results suggest that the 117-gene panel could be a valuable tool also in the differential diagnosis of B-MPM. In fact, we reached a good diagnostic sensitivity (current diagnostic sensitivity on cytology ranges from 30 to 75%) with a classification model built on E-MPM using similarities between these histotypes. It is likely that the analysis of more cases will allow to a) define a classification model on B-MPM thus improving the performance, b) determine how the percentage of sarcomatoid component influence the classification and c) evaluate whether the same tool could help discriminate also E-MPM from B-MPM effusions, since among the 117 genes there are some MPM histotype specific markers.

Keywords: Biphasic Mesothelioma, Pleural effusions, Differential diagnosis, Gene expression, Cytology
**MS01.04: Case Series Exploration of Early Mesothelioma in Pleural Effusions: The Significance of BAP1 Immunohistochemistry and CDKN2A/p16 Fluorescence in Situ Hybridisation**

Louw A1,2,3,4, Peverall J5, Van Vliet C2, Creaney J3,4,6, Lee G4,5,7, Chai S2

1Edith Cowan University, Perth, Australia, 2Department of Anatomical Pathology, PathWest Laboratory Medicine, Perth, Australia, 3National Centre for Asbestos Related Diseases, University of Western Australia, Perth, Australia, 4Institute for Respiratory Health, Nedlands, Australia, 5Department of Diagnostic Genomics, PathWest Laboratory Medicine, Perth, Australia, 6Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Nedlands, Perth, Australia, 7School of Medicine, University of Western Australia, Nedlands, Perth, Australia

Parallel Mini-Symposia 01: Pathology, Virtual, May 7, 2021, 2:30 PM - 4:00 PM

**Objectives:** Western Australia has one of the highest rates of malignant pleural mesothelioma (MPM) per capita in the world, with most cases being diagnosed by cytology at our institution. Guidelines for the cytological diagnosis of MPM were first set out by the International Mesothelioma Interest Group (IMIG) and endorsed by the International Academy of Cytology (IAC) in 2015. Recently, the concept of mesothelioma in situ (MIS) has been re-explored in a small case series. Using more recent ancillary investigations exploiting the most common genetic aberrations in the disease, Churg et al stipulated the loss of BAP1 expression in the surface mesothelium for a diagnosis of MIS to be made. Deletion of CDKN2A/p16 by FISH was found to be rare and was hypothesized to represent a later genetic event. Our objective was to assess the patterns of expression of BAP1 by immunohistochemistry (IHC) and CDKN2A/p16 by fluorescence in situ hybridisation (FISH) in pleural fluid samples taken prior to a definitive diagnosis of mesothelioma at our institution.

**Methods:** All cases of MPM diagnosed at PathWest between 2010 and June 2019 were identified following retrospective review of SNOP codes in the database. Those patients that had a pleural effusion sample submitted for pathological review at least 2 years before definitive diagnosis were identified. Retrospectively, BAP1 staining was performed by immunohistochemistry (IHC) and CDKN2A/p16 assessment by fluorescence in situ hybridisation (FISH). All slides were reviewed by two pathologists independently.

**Results:** Eight patients were identified that met the above criteria. These initial fluid samples were designated ‘negative for malignancy’ in five cases and ‘atypical or suspicious mesothelial proliferation’ in three cases. The average age at diagnosis was 68 years (50-86 years) and one patient was female. The average time between the initial sample and that allowing a definitive diagnosis was 41 months (24-56 months). The average survival time from the initial procedure was 73 months (40 -141 months). BAP1 loss was identified in 6 of 8 cases, while CDKN2A/p16 homozygous deletion was found in 1 of 7 cases with sufficient sample for analysis.

**Conclusion:** In 7 of 8 cases either BAP1 loss or CDKN2A/p16 homozygous deletion was detected. These cases demonstrate that even in pleural fluid samples that do not meet cytological criteria for a diagnosis of mesothelioma, ancillary investigations are able to highlight genetic changes years prior to definitive cytopathological or histological diagnosis.

**Keywords:** mesothelioma, mesothelioma in situ, BAP1, CDKN2A, cytology

---

**MS01.05: Cytological Variants of Epithelioid Malignant Pleural Mesothelioma: Incidence, Prognosis and Association with Nuclear Grade**

Zhang Y1,2, Brambilla C2, Rice A2,3, Robertus J2,3, Molyneaux P3,4, Jordan S4, Lim E3,5, Lang-Lazdunski L6, Popat S3,7,8, Moffatt M1,3, Cookson W1,3, Nicholson A2,3

1National Centre for Mesothelioma Research, National Heart and Lung Institute, Imperial College London, London, United Kingdom, 2Department of Histopathology, Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom, 3National Heart and Lung Institute, Imperial College London, London, United Kingdom, 4NIHR Respiratory Clinical Research Facility,
Parallel Mini-Symposia 01: Pathology, Virtual, May 7, 2021, 2:30 PM - 4:00 PM

Objectives: Cytological variants of epithelioid malignant pleural mesothelioma (E-MPM) are well recognised yet, unlike nuclear grade and growth patterns, their incidences and prognostic impact are less well studied. It is also uncertain if prognostic relevance is independent of nuclear grade.

Methods: We retrospectively reviewed a previously characterised cohort of 614 cases of E-MPM diagnosed over a 15-year period, for which clinicopathological parameters including 2-tier nuclear grade have been evaluated. The diagnostic criteria for clear cell, signet ring, deciduoid, rhabdoid and small cell variants were extracted from the literature and agreed upon by the reviewing pathologists. No minimal cut off threshold was employed. Survival analysis was performed using Kaplan-Meier method.

Results: Cytological variants were seen in 32.4% of cases (199/614). Clear cell variant (13.0%, 80/614) was associated worse median overall survival (OS) than E-MPM without (11.1 vs. 14.7 months, p<0.001) and predicted survival independent of age, type of procedure, atypical mitosis and 2-tier nuclear grade (HR 1.43, p=0.005). Rhabdoid cell variant was shown to be rare (3.3%, 20/614) but highly aggressive (Median OS 5.2 vs. 14.7 months, p<0.001), being almost exclusively seen in high grade and pleomorphic E-MPM (p<0.001). Deciduoid cell variant was the most common cytological variant (17.1%, 105/614), however despite being associated with high grade and pleomorphic E-MPM (p<0.001), was not prognostically significant in univariate setting (Median OS 11.1 vs. 14.7 months, p=0.074). Small cell variants was the least common (0.3%, 2/614) and both cases were histologically high grade (OS 3.3 and 5.9 months respectively). Signet ring cell variant (5.4%, 33/614) was not shown to be prognostically significant (17.6 vs 14.0 months, p=0.808) and was seen across nuclear grades (p=0.474).

Conclusion: Our study showed clear cell, but not rhabdoid cell variant is an independent predictor of worse overall survival in E-MPM. These findings warrant independent validation.

Keywords: Mesothelioma, cytological variant, clear cell, rhabdoid, nuclear grade
MS01.06: Difference in Morphology Between Germline Mutated Malignant Mesotheliomas and Sporadic Malignant Mesotheliomas

Chen H1, Gadiraju M1, Churpek J2, Kindler H1, Hung Y3, Mino-Kenudson M3, Attanoos R4, Schulte J1, Mueller J1, Krausz T1, Husain A1

1University Of Chicago Hospitals, Chicago, United States, 2The University of Wisconsin School of Medicine and Public Health, Madison, United States, 3Massachusetts General Hospital and Harvard Medical School, Boston, United States, 4University Hospital of Wales, Cardiff, The United Kingdom

Parallel Mini-Symposia 01: Pathology, Virtual, May 7, 2021, 2:30 PM - 4:00 PM

Introduction: Some individuals with predisposing inherited mutations develop malignant mesothelioma (MM). According to published literature, germline mutated MMs, especially those with BAP1 mutations, have a longer survival time and appear to be more indolent. This study aims to compare the morphology of MMs with germline mutations to those without.

Materials and Methods: Eligible patients with pathologically confirmed MM underwent panel-based hereditary cancer susceptibility germline genetic testing. Control groups were matched by MM histologic type, location, age, and sex. Nuclear grade (3-tiers comprised of mitotic count and nuclear atypia) and the presence of necrosis (yes/no) were compared via Fisher’s Exact and Chi-Squared Tests.

Results: We identified 40 MM patients with a germline mutation, including 35 of 265 MM patients prospectively tested at a single institution and 5 patients from two additional institutions. Of the 40 MMs, 34 had histologic subtype recorded: 32 were epithelioid MM (E-MM), 2 were biphasic MM, and none were sarcomatoid. There were 11 gene variants with BAP1 being most common (n=12). There were 15 peritoneal cases, 15 pleural cases, and 3 bi-cavitary cases. The average survival time for germline mutated MMs was 33 months and the average survival time for non-germline mutated MMs was 28 months. Amongst E-MMs, there was no difference in nuclear grade or presence/absence of necrosis between germline mutated MMs and non-germline mutated MMs (p=0.22, p=1, respectively). The most common architectural patterns in both groups were solid and trabecular.

Discussion: Germline mutated MMs are extensively E-MM but do not show distinguishing morphologic features as compared to non-germline mutated E-MMs. Survival time is improved in germline mutated MM patients. Germline testing should be driven by clinical suspicion.

Keywords: pathology, germline mutation, BAP1, epithelioid, morphology
ABSTRACTS

**MS01.07** The Potential Contribution of Hexavalent Chromium to the Carcinogenicity of Chrysotile Asbestos

**Walter M**¹, Schenkeveld **W**², Schelch **K**³, Peter-Vörösmarty **B**³, Kraemer **S**¹, Grusch **M**³

¹University Of Vienna, Centre for Microbiology and Environmental System Science, , Austria, ²Wageningen University, Soil Chemistry and Chemical Soil Quality group, , the Netherlands, ³Medical University of Vienna, Institute of Cancer Research, , Austria

**Parallel Mini-Symposia 01: Pathology, Virtual, May 7, 2021, 2:30 PM - 4:00 PM**

**Objectives:** Asbestos refers to a group of carcinogenic minerals that have abundantly been used in industrial and consumer applications. Chrysotile asbestos accounts for >95% of the total historic asbestos use. The carcinogenicity of asbestos is partly governed by the chemical reactivity of the fiber surfaces. The fibers’ ability to generate highly reactive oxygen radical species from extracellular hydrogen peroxide (H₂O₂) has been extensively investigated in this context. Additionally, chrysotile contains trivalent Cr (Cr(III)), up to the permille range. Hexavalent chromium (Cr(VI)) is a potent genotoxic carcinogen in humans and induces lung carcinoma upon inhalation. We hypothesized that at the physiologic lung pH 7.4, Cr(III) in chrysotile can oxidatively dissolve from the fibers as Cr(VI) by H₂O₂ (which is abundant in inflamed tissues), and that the leached Cr(VI) can be absorbed in cells of asbestos-burdened respiratory tissues.

**Methods:** Leaching of Cr from pristine and artificially aged chrysotile asbestos was studied at pH 7.4 in batch dissolution experiments in the presence and absence of H₂O₂; leached Cr was quantified by ICP-OES. Speciation of the detected chromium was determined by chemical equilibrium modelling. Cr(VI) uptake into cells of typically asbestos-burdened tissues was studied in a manner of increasing biological complexity; representative lung epithelial, lung cancer, mesothelial and mesothelioma cells were selected for that purpose. First, expression of the Cr(VI)-transporting anion exchangers SLC4A1 and SLC26A1 was studied by RT-PCR in cell lines of these four tissues. Furthermore, genome-wide transcriptomic analyses of mesothelial and mesothelioma cells were screened for expression of these two transporters. Then, the proteins of both SLC genes were detected in cell lines of these tissues by specific antibody binding and subsequent western blot analyses. Finally, Cr(VI) uptake into cells of these tissues was tested in cell-incubation experiments with subsequent ICP-MS measurement of intracellular Cr.

**Results:** Cr(VI) leached from pristine and artificially aged chrysotile, but exclusively in the presence of H₂O₂. SLC4A1 and SLC26A1 expression was detected in all investigated cells of potentially asbestos burdened respiratory tissues. In agreement with that, Cr(VI) uptake was verified in all conducted cell-incubation experiments; intracellular location of the detected Cr was demonstrated by including potent anion transporter inhibitors in the cell incubation experiments.

**Conclusions:** This work demonstrates that Cr(VI) might potentially contribute to the pathogenesis of asbestos-related malignancies based on chemical (oxidative dissolution of Cr(VI) by extracellular H₂O₂) and biological (Cr(VI) uptake in cells of asbestos burdened tissues) considerations. Whereas Cr(VI) is an established carcinogen in human lung cancer pathogenesis, our work suggests that Cr(VI) leaching from asbestos could also be relevant in the pathogenesis of asbestos-related lung carcinomas and mesotheliomas.

Chrysotile asbestos, hexavalent chromium, mesothelioma, lung carcinoma, hydrogen peroxide, mesothelium

**MS01.08:** Is MTAP Expression an Adequate Surrogate of CDKN2A (p16) Homozygous Deletion? Cross-Validation From the Experience of the MESOPATH Reference Center

**Brcic L**¹, Le Stang **N**², Gallob **F**¹, Pissaloux **D**³,⁴, Sequeiros **R**², Tirode **F**⁴, Paindavoine **S**³,⁴, Pairon **J**³, Dacic **S**⁵, Girard **N**², Churg **A**², Galateau Salle **F**²,³

¹Diagnostic and Research Institute of Pathology, Medical University of Graz, Graz, Austria, ²MESOPATH College, MESONAT, MESOBANK, Department of BioPathology Centre Léon Bérard, Lyon, France, ³Department of Biopathology, Unit of Molecular Pathology and Cancer Research Center of Lyon, INSERM U1052-CNRS5286,
Laon, France, \textsuperscript{4}Team Genetics, Epigenetics and Biology of Sarcomas, Univ Lyon, Université Claude Bernard Lyon 1, INSERM 1052, CNRS 5286, Cancer Research Center of Lyon, Centre Léon Bérard, Lyon, France, \textsuperscript{5}INSEERM U955, équipe 4, UPEC, Faculté de médecine et CHU Creteil, Service de Pathologies professionnelles et de l’Environnement, IST-PE, Creteil, France, \textsuperscript{6}Department of Pathology University of Pittsburgh, Pittsburgh, USA, \textsuperscript{7}EURACAN and Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France, \textsuperscript{8}Department of Pathology, Vancouver General Hospital and University of British Columbia, Vancouver, Canada

**Parallel Mini-Symposia 01: Pathology, Virtual, May 7, 2021, 2:30 PM - 4:00 PM**

**Objectives:** Distinguishing reactive mesothelial lesions from malignant mesothelioma based on morphology alone is always a challenge. The homozygous deletion of the locus 9p21 is one of the most recurrent abnormalities after BAP1, observed in more than 70% of malignant pleural mesotheliomas (MPM). This locus contains among others a CDKN2A (p16) gene and MTAP. 9p21 homozygous deletion, detected by fluorescence in situ hybridization (FISH), is 100% specific for malignant mesothelioma with an average 64% sensitivity. However, concordance of p16 immunohistochemistry with FISH analysis shows some discrepancies. Recent studies comparing MTAP immunohistochemistry with CDKN2A (p16) deletion by FISH analysis demonstrated high concordance. This study aimed to analyze the correlation between MTAP and p16 protein expression among the three conventional histologic subtypes of MPM, with 9p21 homozygous deletion by FISH.

**Methods:** Cases were selected from the French mesothelioma clinical-biological database (MESOBANK), with a diagnosis of MPM validated by the College of pathologists MESOPATH according to 2015 WHO classification. All three main histologic types of MPM were represented in proportions representing the real-world incidence. Expression of p16 and MTAP was analyzed and assessed as the percentage of (nuclear and cytoplasmic) positive tumor cells. Dual-color FISH for CDKN2A deletion was performed using the ZytoVision probes for the CDKN2A locus (9p21) and the centromere of the chromosome 9 (CEP-9).

**Results:** Altogether, 53 cases with 9p21 homozygous deletion (HD), 39 cases with heterozygous deletion (HeD), and 33 cases without deletion (NoD) were analyzed. Amongst the cases with confirmed CDKN2A HD (n=53), 96% had p16 nuclear expression loss when applying a 1% cut-off, demonstrating a high sensitivity of p16 staining. However, p16 expression was also negative in 43% of the cases without evidence of CDKN2A deletion (p<0.0001) demonstrating a low specificity. Cytoplasmic MTAP expression (cut-off 30%) was lost in 86% of the cases with CDKN2A HD but retained in 85% of the cases without the CDKN2A HD. The combination of p16 nuclear (cut-off <1%) and MTAP cytoplasmic (cut-off of <30%) losses demonstrated both high specificity (96%) and high sensitivity (86%) for CDKN2A HD detection. Patients with p16 HD had a worse prognosis, while no statistical difference was observed in HeD vs NoD group.

**Conclusion:** Our results support the routine use of MTAP immunohistochemical expression as a validated surrogate marker for CDKN2A HD. Moreover, when FISH cannot be performed, to obtain the highest levels of sensitivity and specificity, the evaluation of the expression of both nuclear p16 and cytoplasmic MTAP is recommended. Our study confirms the worse prognosis observed in patients with p16 HD and supports the idea that HeD should not be used for a diagnosis of malignancy.

malignant pleural mesothelioma, p16, CDKN2A, MTAP, immunohistochemistry, FISH

**MS02.04: Preliminary Results of the Phase 2 Portion of the ATOMIC-meso Study Comparing ADI-PEG20 or Placebo with Pemetrexed and Cisplatin in Patients with ASS1-deficient Non-epithelioid Mesothelioma**


1Barts Cancer Institute, London, United Kingdom

**Parallel Mini-Symposia 02: Clinical Trials, Virtual, May 7, 2021, 2:30 PM - 4:00 PM**

**Objectives:** Non-epithelioid malignant pleural mesothelioma (MPM) has a poor prognosis but is...
sensitive to arginine deprivation due to frequent loss of argininosuccinate synthetase 1 (ASS1). In the TRAP Phase 1 trial (NCT02029690) ADI-PEG 20 combined with 1st-line pemetrexed (PEM) and cisplatin (CDDP) chemotherapy revealed a 94% disease control rate (34/36) in MPM with a 33.3% partial response rate in biphasic and sarcomatoid subtypes. The ATOMIC-meso study was designed to assess the efficacy of ADI-PEG20 or placebo combined with PEM and CDDP in patients with non-epithelioid MPM in a randomized, placebo-controlled, double-blind, biomarker adaptive-design, phase 2/3 global trial. Here, we report the preliminary findings in the phase 2 portion of ATOMIC-meso.

**Methods:** Enrolment of 176 good performance (ECOG 0-1) patients with non-epithelioid MPM was planned in the phase 2 study with retrospective testing for ASS1 expression by immunohistochemistry. Patients were randomized to receive weekly ADI-PEG20 (36 mg/m² IM) or placebo with standard doses of PEM and CDDP for a maximum of 18 weeks (6 cycles) of treatment. Patients who developed CDDP toxicity were switched to carboplatin. Maintenance ADI-PEG20 or placebo was allowed upon completion of PEM and platinum. Treatment response was evaluated using blinded independent central review (BICR) every 6 weeks by modified RECIST or for patients with significant extrathoracic disease, RECIST 1.1. The primary endpoint for the phase 2 was the overall response rate (ORR) with secondary endpoints of progression-free and overall survival (PFS and OS), safety and toxicity. The phase 2 ORR proportions with the placebo triplet was set at 15% vs. 35% for the ADI-PEG20 triplet, with a 1:1 randomization, 80% power.

**Results:** 169/176 patients (biphasic 46%; sarcomatoid 54%) have been recruited as of Oct 2019, with full accrual of the phase 2 portion of ATOMIC-meso expected by the end of Nov 2019. The ORR by BICR is 20% (n=30/150). The overall median PFS is 5.9 months (95% CI: 5.4, 7.9) and the overall median OS is 8.7 months (95% CI: 6.5, 10.9). As expected, there is a statistically significant survival difference for patients with biphasic compared with sarcomatoid subtypes, namely 11.8 (95% CI: 8.3, 19.3) and 5.7 (95% CI: 4.5, 8.7) months, respectively (p<0.005). No additional safety concerns have been identified.

**Conclusion:** ATOMIC-meso is the largest first-line triplet chemotherapy study to assess the role of targeted arginine deprivation in aggressive subtypes of mesothelioma on a global scale (US, Europe, and Australasia). The overall blinded data is encouraging and an interim analysis for ORR is planned once the 176 patients have reached the first CT treatment response assessment scan. Pending a Go decision, a total of up to 386 patients will be randomized to complete ATOMIC-meso (NCT02709512).

**Keywords:** arginine, ASS1, ADI-PEG20, non-epithelioid mesothelioma, ATOMIC-meso study, phase 2/3

**Table 1:** Summary of Adverse Events

<table>
<thead>
<tr>
<th>AE Name</th>
<th>Grade</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chest wall pain</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Night sweats</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Radiation hepatitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Subcutaneous fibrosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Numbness at surgical site</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Sacral ulcer</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Spinal Stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>17</td>
</tr>
</tbody>
</table>

malignant pleural mesothelioma, pleurectomy/decortication, oligofractionation, clinical trials, multimodality treatment
**MS02:05: Surgery for Mesothelioma After Radiation Therapy using Extensive Pleural Resection (SMARTER): Preliminary Results**

Cho J1, Bradbury P1, Donahoe L2, Hope A1, de Perrot M2

1Princess Margaret Cancer Centre, Toronto, Canada, 2Toronto General Hospital, Toronto, Canada

**Parallel Mini-Symposia 02: Clinical Trials, Virtual, May 7, 2021, 2:30 PM - 4:00 PM**

**Objectives:** Surgery for Mesothelioma After Radiation Therapy (SMART) study was recently published and showed improved overall survival in selected malignant pleural mesothelioma (MPM) patients treated with neoadjuvant hemithoracic radiation therapy (RT) followed by extra-pleural pneumonectomy (EPP) compared to historical series. Unfortunately, SMART’s morbidity limited its widespread deployment. We, thus, developed SMARTER to reduce treatment-related morbidity. The primary aim is determine the maximum tolerated dose (MTD) for the Background and Boost RT regimen before pleurectomy-decortication (PD). We hereby report our preliminary results.

**Methods:** SMARTER is a REB approved 3+3 phase 1 prospective cohort clinical trial. Patients with clinically resectable T1-3N0-1M0 MPM are eligible. The starting cohort (n=3) received a neoadjuvant Background hemithoracic dose to the affected hemithorax of 0 Gy with concomitant Boost dose (of at least 21 Gy) to a part of the GTV. The radiation is delivered over 3 alternate days over 5-7 calendar days followed by extended PD after 7 to 14 days. If no DLTs seen, then the Background hemithoracic RT dose is increased by 6 Gy (up to 18 Gy) and the cohort (n=3) for the next dose level will be accrued as per the usual 3+3 design. An expanded phase II study is planned once maximum tolerated Background dose is reached. Toxicities are graded according the CTCAE v5.0 criteria. Patients are followed clinically and radiologically with CT scans.

**Results:** This is a clinical trial in progress. A total of 6 patients (4 males, 66±11 years old, 3 right sided tumors) were accrued between 09/2019 and 11/2020. We successfully completed the first 2 cohorts (0 and 6 Gy) and are accruing the 3rd (n=2). All patients completed IMRT and EPP. RT was well tolerated with no dose limiting toxicity (Table 1). EPP was performed 10±2 days after completion of IMRT. No patients died within 30 days of surgery or in-hospital. Pathological stage was ypT3N1M0 (n=2), ypT3NxM0 (n=1), ypT2N0M0 (n=2) and pending (n=1). Post-operative histology was: biphasic (n=1), epithelioid (n=4), pending (n=1). There were 2 grade 3 toxicities seen: constipation, and spinal stroke (left leg weakness post-op day 4, MR spine showed spinal cord infarction). Few adverse events were attributable to treatments: definitively (2 RT; 1 surgery), probably (4 RT; 7 surgery). None of the grade 3 toxicities are attributable to either IMRT or EPP.

**Conclusion:** After first 2 cohorts, dose limiting toxicity for SMARTER has not been reached. We are continuing to accrue to this study.
**MS02.06: Phase II Study of PARP Inhibitor Olaparib in Patients with Malignant Mesothelioma**

Hassan R, Mian I, Sengupta M, Thomas A, Steinberg S, Ghafoor A

1Thoracic and GI Malignancies Branch, National Cancer Institute, National Institutes of Health, Bethesda, United States, 2Developmental Therapeutics Branch, National Cancer Institute, National Institutes of Health, Bethesda, United States, 3Biostatistics and Data Management Section, National Cancer Institute, National Institutes of Health, Bethesda, United States

Parallel Mini-Symposia 02: Clinical Trials, Virtual, May 7, 2021, 2:30 PM - 4:00 PM

**Objectives:** BRCA1 associated protein-1 (BAP1), a nuclear deubiquitinase involved in homologous recombination mediated DNA-double-strand repair, is frequently mutated in patients with malignant mesothelioma (MM). Since BRCA1/2 mutant ovarian and breast cancers are highly sensitive to poly-(ADP-ribose) polymerase inhibitors (PARPi), as well as our pre-clinical studies demonstrating sensitivity of mesothelioma cells to PARPi, we sought to evaluate efficacy of olaparib in MM patients based on the somatic or germline mutation status of DNA repair genes.

**Methods:** This single center Phase II study enrolled patients with advanced pleural or peritoneal mesothelioma who had progressed on prior therapies that included a platinum and pemetrexed treatment regimen (Clinical Trial identifier: NCT03531840). Eligibility criteria included patients older than 18 years of age, ECOG performance status of <1 and adequate organ and bone marrow functions. Patients received olaparib, 300mg po bid administered continuously in 3-week cycles with dose reductions allowed for hematologic toxicities or renal dysfunction. Efficacy was assessed by CT scan every 6 weeks using RECIST criteria. Primary objective of the study was to determine the efficacy of olaparib with respect to objective response rate in patients with malignant mesothelioma based on somatic or germline mutation status of DNA repair genes. Secondary objectives include safety and tolerability of olaparib and overall survival.

**Results:** Between July 2018 to October 2019, 23 patients were enrolled and treated, 15 with pleural and 8 with peritoneal disease. Of these, 14 were male and 9 were female. Median age of the patients at enrollment was 63 years (range 41-75 years). Median number of prior treatments was 3 (range 1-5). Seventeen of 23 patients had available tumor tissue for whole exome sequencing and all the patients underwent germline sequencing for identification of pathogenic mutations in DNA repair genes.

**Conclusion:** Olaparib was well tolerated by the patients. As of October 28, 2019, one patient is receiving study drug and 22 are off study treatment. Analysis of the clinical and sequencing data is ongoing. The anti-tumor efficacy of olaparib and its correlation with both somatic and germline mutations status of the patients will be presented.

**MS02.07: Searching for Enrolment for MARS-2: A United Kingdom Cancer Network’s Specialist Mesothelioma MDT Screening Experience**


1Northern General Hospital, Sheffield, United Kingdom

Parallel Mini-Symposia 02: Clinical Trials, Virtual, May 7, 2021, 2:30 PM - 4:00 PM

**Objectives:** Surgical trials for malignant pleural mesothelioma are complex and require close co-ordination between specialist and non-specialist centres. In the United Kingdom, specialist mesothelioma multidisciplinary teams (SM-MDTs) are recommended to offer patients the optimal management opinion and enhance recruitment to clinical trials. We present our SM-MDT experience of screening and recruitment to MARS-2, a randomised trial of chemotherapy alone versus chemotherapy with extended pleurectomy-decortication.

**Methods:** Every patient diagnosed with MPM within our geographic area of 1.8 million population was discussed at the SM-MDT and screened for eligibility regarding MARS-2. The screening data obtained over the first 38 months of MARS-2 recruitment are presented, together with data from patients referred from other regional oncology
centres across England. The survival between those eligible and randomised (group 1), eligible but withdrew prior to randomisation (group 2), eligible but declined randomisation (group 3) and ineligible (group 4) was analysed.

Results: Between 12/6/15 and 1/8/18, the SM-MDT screened 301 patients. 49% were ineligible for MARS-2 and 21% were eligible but declined participation. 30% were enrolled. From the 99 patients enrolled, 30% were not randomised, 70% went on to participate in the trial.

Median overall survival varied significantly between the 4 groups. Group 1; 28.9 months, Group 2; 12.6 months, Group 3; 15.7 months, Group 4; 7.4 months, p<0.001 (figure 1). Hazard ratios (HR) were calculated with respect to Group 1, patients who were enrolled and randomised in the study. HR for Group 2; 1.91 (95% confidence interval 1.09-3.33), p=0.02. HR for Group 3; 1.70 (95% confidence interval 1.08-2.65), p=0.02. HR for Group 4; 3.52 (95% confidence interval 2.39-5.20), p<0.001.

Conclusion: Approximately 50% of patients with MPM may be suitable for enrolment in the MARS-2 trial. However, only 39% of eligible patients were enrolled and proceeded to randomisation. Examination of this data may help to identify strategies to optimise recruitment and retention of patients through to randomisation. The SM-MDT allows systematic identification of eligible patients for MARS-2, but challenges remain to retain patients through to randomisation.
MS02:08: First-Line Nivolumab Plus Ipilimumab Versus Chemotherapy in Unresectable Malignant Pleural Mesothelioma (MPM) in CheckMate 743


1Royal Marsden Hospital; Institute of Cancer Research, London, United Kingdom, 2University of Lille, CHU Lille, INSERM U1189, OncoTHAI, Lille, France, 3H. Lee Moffitt Cancer Center, Tampa, United States, 4Hospital Cote De Nacre CHU Caen, Caen, France, 5Centro Medico Nacional Siglo XXI, Mexico City, Mexico, 6Erasmus MC Cancer Institute, Rotterdam, Netherlands, 7Aix Marseille Univ, APHM, Marseille, France, 8Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Italy, 9Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland, 10Centro Oncologico, Medica Sur, Mexico City, Mexico, 11Monash Medical Centre, Clayton, Australia, 12Medical School, Dicle University, Diyarbakir, Turkey, 13Centre Hospitalier Universitaire de Toulouse, Universite Paul Sabatier, Toulouse, France, 14Royal Cornwall Hospital, Royal Cornwall Hospitals NHS Trust, Truro, United Kingdom, 15Medical School, University of Western Australia, Perth, Australia, 16University Paris-Diderot, Paris, France, 17Okayama Rosai Hospital, Okayama, Japan, 18Anderson Cancer Center, Houston, United States, 19Lausanne University Hospital, Lausanne, Switzerland, 20Mayo Clinic, Rochester, United States, 21Adelphi Values, Boston, United States, 22Bristol Myers Squibb, Princeton, United States, 23Health Outcomes Solutions Ltd, London, United Kingdom, 24The Netherlands Cancer Institute and Leiden University Medical Center, Amsterdam, Netherlands

**Objective:** MPM is a highly aggressive cancer with a 5-year survival rate of <10%. Standard-of-care treatment with platinum/pemetrexed chemotherapy (chemo) was approved in 2004. Blockade of the programmed death-1 pathway alone with nivolumab or in combination with cytotoxic T lymphocyte–associated antigen-4 blockade with ipilimumab has shown activity in previously treated patients with MPM. Here we report clinical and patient-reported outcomes (PROs) from CheckMate 743 (NCT02899299), a randomized, phase 3, open-label study evaluating first-line (1L) nivolumab plus ipilimumab versus chemo in MPM.

**Methods:** Adults with unresectable MPM, previously untreated with systemic therapy, and ECOG status 0–1 were randomized 1:1 (stratified by histology [epithelioid versus non-epithelioid] and sex) to receive nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks for a maximum of 2 years, or chemo (cisplatin [75 mg/m²] or carboplatin [AUC 5] plus pemetrexed [500 mg/m²]) for 6 cycles. Overall survival (OS) was the primary endpoint; safety and PROs were exploratory endpoints. The Lung Cancer Symptom Scale (LCSS)-Meso average symptom burden index (ASBI) and 3-item global index were used to evaluate disease-related symptom burden; the EQ-5D-3L visual analog scale (VAS) and utility index were used to evaluate quality of life (HRQoL). PROs were assessed prior to each nivolumab or chemo dose for 12 weeks, every 6 weeks for the following 12 months, then every 12 weeks, and at specified follow-ups.

**Results:** Baseline characteristics were similar between nivolumab plus ipilimumab (n=303) and chemo (n=302) arms. After minimum follow-up of 22.1 months, median OS was 18.1 months with nivolumab plus ipilimumab versus 14.1 months with chemo (HR, 0.74; 95.6% CI, 0.60–0.91; P=0.002); 2-year OS rates were 40.8% versus 27.0%. Median OS was 18.7 versus 16.5 months (HR, 0.86; 95% CI, 0.69–1.08) and 18.1 versus 8.8 months (HR, 0.46; 95% CI, 0.31–0.68) in patients with epithelioid and non-epithelioid histology, respectively; as expected, the effect of chemo was better in epithelioid compared with non-epithelioid histologies. The safety profile was consistent with the known profile of nivolumab plus ipilimumab. Mean LCSS-Meso ASBI scores trended to improve over time from baseline with nivolumab plus ipilimumab but deteriorated with chemo; mean changes did not meet clinically important difference thresholds (±10 score change). With nivolumab plus ipilimumab, mean EQ-5D-3L VAS scores improved over time and reached UK population reference values (norms). With both on-treatment and follow-up assessments, nivolumab plus ipilimumab significantly delayed deterioration in
HRQoL; there was a trend toward symptom delay versus chemo. Similar trends toward improvement in symptom burden and HRQoL with nivolumab plus ipilimumab were observed within the histology subgroups.

**Conclusion:** Previously reported clinical data showed significantly improved OS with nivolumab plus ipilimumab versus chemo in 1L treatment of unresectable MPM; no new safety signals were observed. Patients who received nivolumab plus ipilimumab versus chemo maintained quality of life and delayed time to definitive deterioration in HRQoL. Taken together, these clinically meaningful results support nivolumab plus ipilimumab as a potential new 1L standard-of-care for patients with unresectable MPM.

Immunotherapy; quality-of-life; symptom burden; overall survival; immune checkpoint inhibitors

**MS03.04: Where There’s a TIL, There’s a Ray: Image Guided X-rays Induce Changes in T-cell Phenotypes in Mesothelioma Tumour Micro-environments**

**Wilson W1,2, Dart S1, Cook A1,2, Nowak A1,2,3**

1National Centre for Asbestos Related Diseases, Nedlands, Australia, 2University of Western Australia, Crawley, Australia, 3Department of Medical Oncology, Sir Charles Gairdner Hospital, Nedlands, Australia

Parallel Mini-Symposia 03: Local and Intrapleural Therapies, Virtual, May 7, 2021, 2:30 PM - 4:00 PM

**Objectives:** To investigate the immune changes in mesothelioma in response to radiotherapy and identify target T cells a subcutaneous murine model of the disease. To attempt to modulate this immune response using checkpoint blockade immunotherapy to increase both localized and off target (abscopal) effects.

**Methods:** Tumours and draining lymph nodes were harvested at days 5, 7, and 10 following 3 fractions of 6Gy irradiation to examine temporal T cell responses to radiotherapy. T cell subtype and expression of immune checkpoint blockade molecules were analyzed using flow cytometry.

In order to identify changes in T cell sub-populations, unsupervised cluster approaches were used to isolate phenotypic cell signatures. Identified populations were then cross validated using traditional manual gating of the flow data.

Based on these results, combinations of checkpoint blockade immunotherapy monoclonal antibodies (anti-PD1, anti-TIM3, anti-CTLA4, and anti-OX40) were given with radiotherapy to determine if local and distal off target tumour response could be increased through synergistic effects in either single or dual tumour mouse models. Analysis was conducted on both the tumour growth kinetics and the tumour free survival in these models across all treatment groups.

**Results:** Both treated and untreated tumours and their corresponding lymph nodes showed changes and trends over the time series demonstrating a strong temporal immune component to this subcutaneous murine model of mesothelioma.

With respect to changes observed due to radiotherapy treatment, we were able to uncover novel population loss of CD4+/FoxP3-/OX40+/PD1+ T cells and CD4+/FoxP3+/OX40+/PD1+ T cells in the tumour microenvironment. We also saw a transient increase in CD4+/CTLA4+/PD1+ cells and a decrease of CD4+/FoxP3-/CTLA4+/OX40+/TIM3+/PD1- in the draining lymph nodes of radiotherapy treated tumours.

When targeting these populations, single agent therapies (anti-PD1, anti-TIM3, anti-CTLA4, or anti-OX40) had little effect on their own but addition of radiotherapy increased survival in single tumour models. When applying this approach to dual tumour models, distal tumour growth became limiting factor and survival benefit compared to single modality controls was lost.

Administering combinations of checkpoint blockade immunotherapy in tandem (anti-PD1, anti-TIM3, or anti-OX40) and adding fractionated radiotherapy demonstrated increased tumour response at the local tumour site. Increased complete tumour response in secondary tumours was also detected but this did not translate to increased survival when compared to single agent immunotherapy with radiotherapy.

**Conclusion:** Combination checkpoint blockade for these targets with radiotherapy did not increase adverse effects and proved to be a potential therapy for murine model of mesothelioma showing increased effectiveness. This
approach still requires validation in additional models of this disease and our group is currently studying the optimization of scheduling treatments to increase response.

**Keywords:** Radiotherapy, Immunotherapy, Machine Learning

**MS03.05: Treatment of Lung-Intact Malignant Pleural Mesothelioma with Whole Pleural Intensity-Modulated Proton Therapy: Toxicities and Clinical Outcomes**

Molitoris J¹, Glass E², Decesaris C¹, Jatczak J¹, Fellows Z³, Badiyan S¹, Rolfo C⁴, Scilla K⁵, Culligan M², Friedberg J², Simone, II C⁶, Miller R¹, Mohindra P¹

¹University Of Maryland Dept of Radiation Oncology / Maryland Proton Treatment Center, Baltimore, United States, ²University of Maryland Dept of Thoracic Surgery, Baltimore, United States, ³National Proton Treatment Center, Washington DC, United States, ⁴Washington University Dept of Radiation Oncology, St. Louis, United States, ⁵University of Maryland Dept of Medical Oncology, Baltimore, United States, ⁶New York Proton Center, New York City, United States

**Parallel Mini-Symposia 03: Local and Intrapleural Therapies, Virtual, May 7, 2021, 2:30 PM - 4:00 PM**

**Objectives:** Significant challenges impede the ability to safely deliver hemi-thoracic pleural irradiation for malignant pleural mesothelioma (MPM). Limited data currently exist on toxicities and outcomes for mesothelioma patients treated with proton therapy to the whole pleura for intact lung MPM. We hypothesize that intensity-modulated proton therapy (IMPT) utilizing pencil-beam scanning proton therapy may facilitate safer delivery of radiotherapy in the definitive and adjuvant settings for lung-intact MPM.

**Methods:** Single institutional IRB approved retrospective evaluation of the first 16 patients with lung intact MPM treated with whole pleural (WP) IMPT intensity modulated proton therapy. Acute and late toxicities were scored based on CTCAE v5.0. Kaplan-Meier was used to estimate local control and overall survival. The first 5 patients had comparative Intensity modulated Radiation Therapy (IMRT) photons plans generated for dosimetric comparison.

**Results:** All patients included completed therapy 6 months prior to data collection and median follow up for survivors was 21.8 months (range: 6.9 - 26.6). Patients were a median of 70 years old and had predominantly epithelial histology (75%), stage III disease (75%), Right-sided (69%) and ECOG 0-1 performance status (56%). Fourteen (87.5%) had prior therapy, all receiving platinum/pemetrexed with a median of 4 cycles and 3 of the 14 also received immunotherapy. They received definitive (75%), adjuvant (6.3%) or salvage after pleurectomy/decortication failure (18.8%) WP-IMPT (Table 1).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, median, (range), y</td>
<td>14 (87.5)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>70 (62 - 87)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (87.5)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12 (75.0)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>L laterality</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>11 (68.8)</td>
</tr>
<tr>
<td>Left</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Epithelial</td>
<td>12 (75.0)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>II</td>
<td>12 (75.0)</td>
</tr>
<tr>
<td>III</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0 - 1</td>
<td>9 (56.3)</td>
</tr>
<tr>
<td>2 - 3</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>Indication for RT</td>
<td></td>
</tr>
<tr>
<td>Inoperable (disease)</td>
<td>9 (56.3)</td>
</tr>
<tr>
<td>Inoperable (patient)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Adjuvant post EPD</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Salvage post EPD</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Prior Treatment</td>
<td></td>
</tr>
<tr>
<td>Chemo (Platinum/Almita)</td>
<td>11 (68.8)</td>
</tr>
<tr>
<td>Chemo &amp; Immunotherapy</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>None</td>
<td>2 (12.5)</td>
</tr>
</tbody>
</table>
Median prescribed WP dose was 50.4 GyE (range 45.0-50.4 GyE) and dose to gross disease ranged 50.0-60.2 GyE). Three patients discontinued WP-IMPT early, two for progressive disease and one for decline of pre-existing multiple sclerosis. Treatment was well tolerated, with acute and subacute toxicities limited to grade 2 nausea (25%), grade 2 esophagitis (25%). Eight (50%) of patients experienced pneumonitis with a median time to onset of 6.9 months (95% CI 3.8 – 10.0 months). For patients with greater than 3 months follow up, 8 of 9 patients developed grade 2-3 pneumonitis (grade 2 in 4 patients and grade 3 in 4 patients). No patients had grade 4-5 toxicities. Overall survival at six months and one year were 62.5% (95% CI: 50.4 - 74.6) and 49.2% (95% CI: 36.5 – 61.9). For the nine patients with an ECOG of 0-1, the 12 and 24 month OS was 87.5% (95% CI: 75.8 – 99.2) and 75.0% (95% CI: 59.7 – 90.3). LC at 6 months was 83.3% (95% CI: 72.5 – 94.1) and 60.8% (95% CI: 45.0 – 76.6) at 12 months (Figure 1). IMPT had statistically significantly decreased mean doses to the contralateral lung (Median 0.3 vs 7.0, p<0.001), heart (median 16.1 vs 23.1, p=0.008), and liver (median 14.9 vs 21.0, p=0.009). There was no difference in contralateral lung volume receiving 20Gy (median 0.6 vs 0.9, ns).

**Conclusion:** Our early experience with WP-IMPT for lung-intact mesothelioma, the largest such report to date, demonstrates that the treatment is well tolerated and can achieve excellent local control at 6 months, with continued follow-up necessary.

**Keywords:** Radiation, Proton Therapy, Mesothelioma
MS03.06: Effects of Photon Radiation on DNA Damage, Cell Cycle, Cell Proliferation, and Apoptosis in Murine and Human Mesothelioma Cell Lines

Keam S1,2, Ebert M3,4, Nowak A1,2, Cook A1,2

1National Centre for Asbestos Related Diseases, Perth, Australia, 2School of Medicine, University of Western Australia, Perth, Australia, 3School of Physics, Mathematics and Computing, Perth, Australia, 4Department of Radiation Oncology, Perth, Australia

Objective: Radiotherapy is widely used to palliate symptomatic lesions in patients with mesothelioma. However, radiotherapy alone does not improve patient survival. There is currently little published data on the specifics of how mesothelioma cells respond to photon irradiation in a dose-dependent manner. Here, we aimed to characterise the cellular responses of murine and human mesothelioma cell lines to different doses of photon radiation, with a long-term aim of optimising a clinically relevant in vivo model in which to study the interaction of radiotherapy and immunotherapy combinations.

Methods: Two murine (AB1, AE17) and three human (BYE, JU and MC) exponentially-growing mesothelioma cell lines were irradiated in 50 mL tubes at room temperature using a Gammacell irradiator (3000 SN 211) at doses of 1, 2, 4, 8, 16, or 32 Gy. Irradiated cells were pulse labelled with bromodeoxyuridine (BrdU) for one hour. BrdU pulse labelling cells were stained with mouse anti-BrdU-PerCP-C5.5 (cell proliferation), mouse anti-γ-H2AX (DNA damage), mouse anti-cleaved PARP-PE (Apoptosis) and 4′,6-diamidino-2-phenylindole (DNA content). Data were collected by flow cytometry, and analysed using Flowjo_V10 (Treestar, OR, USA).

Results: The level of DNA damage (γ-H2AX) increased as the radiation dose increased and reached a maximum level at approximately 8 Gy for all studied cell lines. Comparison of the DNA damage responses of murine and human mesothelioma cell lines demonstrated a difference in ED50 (50% DNA damage) between AB1 vs. MC (p=0.009) and BYE vs. MC (p=0.01). We also observed a temporary cell cycle arrest at G2/M phase following 8 Gy radiation at 24 hrs for AB1 cell line; however, doses of 16 and 32 Gy completely arrested the cell cycle of both murine cell lines at G2/M phase. In addition, all murine and human mesothelioma cell lines repaired DNA more efficiently following lower doses (1 or 2 Gy) than following 8, 16 or 32 Gy. All studied cell lines had similar DNA repair. The inhibition of cell proliferation by radiation required at least 8 Gy from 24 hours, and cell proliferation was different between murine and human cell lines. We found a dose-response for apoptosis in the AB1 and BYE cells; in other cell lines this was not the case, with the highest level observed approximately being 5% from 16 Gy at 72 hrs. The comparison of apoptosis demonstrated BYE had higher apoptosis than MC (p=0.03) and AE17 (p=0.04).

Conclusion: Our present study demonstrated different cellular responses in cell proliferation, apoptosis and cell cycle arrest between murine and human mesothelioma cell lines, whilst DNA repair was similar among all studied cell lines. Given increased DNA damage, reduced proliferation and increased apoptosis at cellular level, doses of 8 Gy and above exerted more damaging effects on mesothelioma cell lines than doses of 1 to 4 Gy. These data will provide a broad picture of the in vitro response of mesothelioma cell lines to photon irradiation, and will guide in vivo experiments by informing the selection of hypofractionated doses to combine with immune checkpoint blockade in in-vivo study.

MS03.07: Does Sparing the Diaphragm Improve Early Outcome From Radical Surgery For Malignant Pleural Mesothelioma?

Lee M1, Durand-Hill M1, Baranowski R1, Hargrave J1, Waller D1

1Barts Thorax Centre, St Bartholomew’s Hospital, London, United Kingdom

Objective: Radical surgery for malignant pleural mesothelioma (MPM) faces the challenge of prolonging survival by obtaining macroscopic complete resection
Complete excision of the diaphragm (phrenectomy) can be technically demanding but muscle-sparing complete excision of diaphragmatic pleura may be even more difficult. Some surgeons argue for phrenectomy in most cases, some for diaphragm sparing even at the expense of a R2 resection. We aimed to evaluate the benefit of diaphragm-sparing MCR as the treatment of choice.

Methods: From a consecutive series of 100 patients [86M:14F, age 68(33-79)] undergoing radical surgery by pleurectomy/decortication for MPM by a singlesurgeon at one institution we identified 17 patients [16M:1F, age 67 (45-77)] in whom MCR had been achieved without phrenectomy. We compared their perioperative outcomes with a control group of 15 patients [14M:1F, age 70 (57-78)] in whom MCR had been achieved with phrenectomy but in whom there was no histological evidence of diaphragm muscle invasion. This group could have undergone muscle-sparing MCR if it had been attempted.

Results: Reoperation for non-diaphragm related complications (chylothorax, PFO) was required in 3 patients. In the remainder diaphragm preservation was associated with shorter air leak and postoperative stay whilst not increasing operating time.

Conclusions: Sparing the diaphragm whilst achieving MCR wherever possible does improve perioperative outcomes from pleurectomy/decortication and therefore should be the intention of surgery.
MS04.04: Efficacy of Irradiation Combined with Intracavitary Cisplatin-fibrin after Lung-sparing Surgery in an Orthotopic Rat Model of Mesothelioma

Kirschner M1, Meerang M1, Lauk O1, Furrer K1, Grgic I2, Orlowski V1, Tschanz F2, Guckenberger M2, Pruschy M2, Weder W1, Opitz I1

1Department Of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland, 2Department of Radiation Oncology, University Hospital Zurich, Zurich, Switzerland

Parallel Mini-Symposia 04: Surgery, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Objectives: Localized treatment after tumor resection in malignant pleural mesothelioma (MPM) is aiming for better local tumor control. Here we tested the safety and efficacy of combination treatment with intracavitary cisplatin-fibrin (cis-fib) plus hemithoracic irradiation (IR), applied after lung sparing surgery, in an orthotopic immunocompetent rat model.

Methods: We randomized male F344 rats into five groups (cis-fib (n=9), 10Gy IR (n=6), 20Gy IR (n=9), cis-fib+10Gy IR (n=6), cis-fib+20Gy IR (n=9)). Sub-pleural (parietal) tumor implantation was performed on day 0 with 1 million syngeneic rat mesothelioma cells (IL45-luciferase). We detected tumor nodule formation in all animals by bioluminescence imaging (BLI) on day 8. Tumors were resected on day 9 followed by treatment with intracavitary cis-fib or NaCl-fib. On day 12, CT guided local irradiation in a single high dose (dose rate: 3Gy/min) of the former tumor region, resembling IMRT in human patients, was applied. We monitored animal’s health status daily and tumor growth every 3 days by BLI.

Results: None of the animals, whether with radiotherapy alone or in combination with cis-fib, showed any signs of pulmonary side effects. None had reduced pulmonary functions, measured by increased breathing or the appearance of blue or white colored ears/extremities/eyes assuming desaturation. No weight loss was observed after 10Gy IR, either alone or in combination with cis-fib. Treatment with a single dose of 20Gy IR or cis-fib+20Gy IR caused weight loss on the day after treatment but all animals regained weight 2 days thereafter. No deterioration of body conditioning or activity score were observed in the immediate post-interventional phase. Regarding efficacy, we detected comparable tumor growth in animals treated with 10Gy IR compared to no IR (cis-fib) group. Thus, we decided to escalate to 20Gy after treating 6 animals/group. Three days after treatment with 20Gy IR (day 15), we detected a significant difference in tumor growth in IR alone compared to cis-fib+IR group (mean tumor growth (%) 539 vs 252; p=0.04). On day 21, there was a significant difference in tumor growth between cis-fib vs cis-fib+IR treated tumors (mean tumor growth (%) 2295 vs 660; p=0.01) (figure1).

Conclusion: Irradiation alone and in combination with local intracavitary cis-fib application in rats is safe up to a dosage of 20Gy. The administration of local 20Gy radiotherapy in combination with cis-fib enhances tumor control while only minimally (and short term) affecting animal’s well-being. These data suggest a promising effect of combined local treatment with cis-fib+IR for MPM.

Keywords: intracavitary treatment, cisplatin, irradiation, local tumor control
**MS04.05: Utilizing Endobronchial Ultrasound for Mediastinal Staging in Pleural Mesothelioma**

Steimer D¹, Gedeon P¹, Tramontozzi P¹, Bueno R¹, Tsukada H¹

¹Brigham And Women’s Hospital, Boston, United States

Parallel Mini-Symposia 04: Surgery, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Objectives: Mediastinal staging for mesothelioma remains an important component of the preoperative workup for patients being considered for surgical resection. Endobronchial ultrasound (EBUS) has been used for staging, but the accuracy of this modality remains largely unknown. We review our institution’s experience with EBUS for staging of pleural mesothelioma.

Methods: Between January 2017 and October 2019, all patients with mesothelioma that underwent EBUS mediastinal staging were retrospectively reviewed. EBUS was performed by a single surgeon at our institution. Stations 4R, 4L and 7 were biopsied in all patients and 11L or 11R was sampled when feasible. Rapid on-site evaluation (ROSE) was not utilized in this series. Cytology was classified as positive, negative, non-diagnostic or containing atypical cells. Nodal stations sampled by EBUS were compared to lymph nodes removed at time of pleurectomy to assess the accuracy of staging. Patients determined to be unresectable at the time of surgery did not have lymph node sampling performed. No patients were excluded from analysis.

Results: Fifty-three patients had mediastinal staging by EBUS for mesothelioma at our institution during the study period. There were nine patients (17%) with positive lymph nodes diagnosed by EBUS; five of these patients had multi-station disease. Composite of all mediastinal lymph nodes sampled by EBUS and diagnostic yield rates are presented in Table 1.

Twenty-nine patients underwent surgical resection and lymph node staging. Comparison of EBUS cytology to pathology from surgical specimens revealed 76% accuracy for all stations sampled. The distribution of mesothelioma subtypes for node negative patients were 59% epithelioid (n=13), 36% biphasic (n=8) and 5% sarcomatoid (n=1). Further analysis of specific nodal stations determined a negative predictive value of 60% for 4R and 90% for 7; station 4L was not sampled at time of pleurectomy.

20% of patients (6/29) had nodal upstaging at the time of resection. Four patients had positive 4R, 7 or 11R nodes that were reported negative on EBUS. Two patients in the series had positive 9 or 10 nodes, these were not sampled by EBUS and no comparison was available.

Conclusion: EBUS is a reasonable modality for mediastinal staging in patients with pleural mesothelioma. The negative predictive value of EBUS at station 7 was 90% and 4R was 60% in our series. Further studies are necessary to determine if EBUS is equivalent to mediastinoscopy in this unique patient population.

Keywords: EBUS, mediastinal staging, pleural mesothelioma

---

**Table 1: EBUS cytology by lymph node station**

<table>
<thead>
<tr>
<th></th>
<th>4R (n=50)</th>
<th>4L (n=51)</th>
<th>7 (n=53)</th>
<th>11R (n=15)</th>
<th>11L (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>5</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>26</td>
<td>22</td>
<td>41</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Non-diagnostic</td>
<td>18</td>
<td>28</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Atypical cells</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diagnostic yield</td>
<td>64%</td>
<td>45%</td>
<td>96%</td>
<td>80%</td>
<td>81%</td>
</tr>
</tbody>
</table>
MS04.06: Anti-PD-1 Therapy after Multimodality Therapy Including Total Pleurectomy in Malignant Pleural Mesothelioma: Updated Analysis

Zhang Y1,2,3, Popat S2,5,10, O’Brien M3, Scherpereel A6, Bouchaab H7, Steele J8, Newsom-Davis T9, Moffatt M1,2, Cookson W1,2, Rice A2,3, Nicholson A2,3, Lang-Lazdunski L4

1National Centre for Mesothelioma Research, National Heart and Lung Institute, Imperial College London, London, United Kingdom, 2National Heart and Lung Institute, Imperial College London, London, United Kingdom, 3Department of Histopathology, Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom, 4Thoracic Surgery, BUPA Cromwell Hospital, London, United Kingdom, 5Royal Marsden NHS Foundation Trust, London, United Kingdom, 6Department of Pulmonary and Thoracic Oncology, Regional University Hospital of Lille, Lille, France, 7Department of Oncology, Lausanne University Hospital / UNIL, Lausanne, Switzerland, 8Department of Oncology, Barts Health NHS Trust, London, United Kingdom, 9Department of Oncology, Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom, 10The Institute of Cancer Research, London, United Kingdom

Parallel Mini-Symposia 04: Surgery, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Objectives: We previously reviewed our experience in selected patients who received Pembrolizumab or Nivolumab following multimodality therapy for malignant pleural mesothelioma (MPM). Here we present updated treatment data and survival analysis for 18 patients.
Methods: This is a retrospective observational study including patients with histologically-proven MPM having completed multimodality therapy and received anti-PD-1 immunotherapy as 2nd or 3rd line treatment. Data were retrieved from a prospective mesothelioma database. Histopathology, BAP1, MTAP and PD-L1 (22C3) immunohistochemistry were performed on surgical specimens and reported by a senior pathologist. All patients had chest computed tomography and positron emission tomography (PET-CT) as part of their normal follow-up. Response evaluation was determined using RECIST 1.1 criteria.

Results: 18 patients received anti-PD-1 immunotherapy between August 2016 and October 2019. All patients had total pleurectomy/decortication, prophylactic radiotherapy (21Gy/3) and systemic chemotherapy based on pemetrexed and platinum. Median age was 66 years, with male predominance (15/18). ECOG performance status was 0 (n=15) and 1 (n=3). 61% (11/18) tumours were epithelioid subtype, and 39% (7/18) were biphasic. Median time to starting immunotherapy was 20.8 months (range 10.5-43.7) following surgery. 14 patients received Pembrolizumab and 4 received Nivolumab. Median number of cycles of anti-PD-1 therapy received was 6 (range 1-33). Disease control rate at 12 weeks was 61.1% and 7 (38.9%) patients had disease progression. Adverse events were observed in 6 patients (one Grade 3). Median OS from diagnosis and the start of immunotherapy was 46.6 and 24.0 months respectively. 4 patients received treatment for 14 months or more. 6 patients started further therapies after discontinuing immunotherapy.

Conclusion: In our cohort, second or third-line anti-PD1 immunotherapy showed efficacy with DCR comparable to non-surgical setting. Further studies are warranted to validate our preliminary findings.

Keywords: Mesothelioma, Multimodality therapy, immunotherapy, PD-1, total pleurectomy/decortication

MS04.07: Postoperative Empyema after Pleurectomy Decortication for Malignant Pleural Mesothelioma

Lapidot M1, Mazzola E2, Bueno R1
1Brigham and Women’s Hospital, Harvard Medical School, Boston, United States, 2Dana Farber Cancer Institute, Harvard Medical School, Boston, USA

Parallel Mini-Symposia 04: Surgery, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Objectives: Postoperative empyema following pleurectomy decortication (PDC) for malignant pleural mesothelioma (MPM) is a serious complication that necessitates prolonged hospitalization. The aim of this study was to determine the incidence and for the first time the risk factors for postoperative empyema in patients undergoing PDC.

Methods: The background, type of PDC, neo-adjuvant treatment, date of empyema, pleural fluid cultures, post empyema treatment, and prognosis from a series of consecutive 355 patients treated over 9 years at a single high-volume center were investigated. Fisher’s exact test, Kaplan Meier estimators, and log rank test were used to identify significant risk factors for postoperative empyema and compare the overall survival.

Results: 355 patients underwent PDC for MPM in a 9-year period. There were 262 males (74%) and the median age at surgery (range) was 69 (30-86). Neoadjuvant therapy was given to 87(24.6%) and 282(79.7%) received intraoperative heated chemotherapy (IOHC). The median hospital length of stay (LOS) was 14 days (1-148). During the study, 24 patients (6.8%) developed empyema. The LOS of patients for patients who developed postoperative empyema was significantly prolonged (median- 24 days, p<0.001). Pleural effusion samples were collected from
all the patients who developed postoperative empyema and included 26 types of bacteria and fungus. MSSA was found in 8 samples, Fungi in 6, MRSA in 2, pseudomonas in 2, α or β hemolytic strep in 2 and other types of bacteria were found in 6 samples. Treatment for empyema included chest drainage in 9 patients, surgical exploration and washout in 8, and surgical creation of Claggett window in 7. Median survival for patients who developed postoperative empyema was 11.7 months while 21.3 months for patients without empyema (HR-1.78, P=0.01). The occurrence rate of postoperative empyema was significantly higher in patients with the following factors: male(p=0.05), prolonged air leak(p<0.001), and use of prosthetic mesh(p=0.03). Age, neo-adjuvant therapy, advance TNM staging, and histology were not associated with a higher incidence of postoperative empyema. In a univariate analysis factors that were found to be associated with better overall survival in patients who developed postoperative empyema included younger age, epithelioid histology, and administration of adjuvant therapy.

Conclusion: Postoperative empyema following PDC for MPM is associated with prolonged length of stay and higher mortality. The rates of this serious postoperative complication might decrease by developing better strategies to avoid prolonged air leak after PDC

Malignant Pleural Mesothelioma(MPM), Postoperative Empyema, Pleurectomy Decortication(PDC), Extended Pleurectomy Decortication(EPDC)

MS05.04: Analysis and Augmentation of the Immunologic Bystander Effects of CAR T Cells in a Malignant Mesothelioma (MM) Syngeneic Mouse Model

Klampatsa A1, Leibowitz M2, Liousia M2, Arquíri E2, Sun J2, Olimpo N2, Wang L3, Jorapur A4, Pookot D4, Brockstedt D4, Hancock W3, Albelda S2

1Cancer Therapeutics, Institute Of Cancer Research, London, United Kingdom, 2Pulmonary, Allergy and Critical Care Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA, 3Children’s Hospital of Philadelphia, Philadelphia, USA, 4RAPT Therapeutics, Berkeley, USA

Objectives: The use of adoptive transfer of T cells transduced with chimeric antigen receptors (CARs) has revolutionized the treatment of hematologic malignancies, however their therapeutic success is limited in the treatment of solid cancers, including MM. Major challenges within the hostile tumor microenvironment, poor trafficking and the presence of inhibitory tumor cells contribute to CAR treatment limitations. In this study, we aimed to look at another obstacle, namely tumor antigen heterogeneity, and whether this can be overcome by CAR T cell induction of bystander effects; meaning, the ability of CAR T cells to eradicate tumor cells not expressing the targeted antigen.

Methods: To undertake this study, a system where 100% antigen-positive MM tumors can be eradicated by mouse CAR T cells in immune competent animals was required. We have thus developed a murine CAR T cell therapy targeted against human mesothelin-expressing MM cells (namely M11 CAR T cells), which is able to cure AE17 murine tumors, stably transduced with human mesothelin and ovalbumin, in immunocompetent mice. Using this model, we mixed mesothelin +ve and -ve AE17 tumor cells to create tumors <100% positive for mesothelin and found that the M11 CAR T cells were unable to cure tumors even when only 10% of the tumor cells were antigen -ve. We then embarked in testing various agents that could augment efficacy of M11 CAR T cells.

Results: Administration of anti-PD1, anti-CTLA-4, anti-TGFβ or agonistic CD40 antibodies, or IDO inhibitor in combination with M11 CAR T cells did not induce bystander effects. However, pre-treatment of the mice with low dose cyclophosphamide (CTX) induced an M11 CAR T cell bystander effect that resulted in cure of mixed mesothelin +ve/-ve tumors. Lymph node and spleen analysis at the end of these studies showed that CTX pre-treatment resulted in persistence of M11 CAR T cells, increased epitope spreading (through measurement of ovalbumin-specific T cells) and a reduction in CD4+ Tregulatory cells (Tregs). Mechanistic studies revealed dependance on endogenous CD8 T cells, but surprisingly BATF3-dependent dendritic cells were not required. However, reduction of Tregs through genetic ablation or blockade of Treg trafficking into tumors using a CCR4 inhibitor (provide by RAPT Therapeutics) augmented CAR T cell efficacy and enhanced bystander effects.
Conclusion: This study, although limited in one tumor/mouse model, provides important information with potential implications in CAR T cell therapy trials. Firstly, the data suggest that CAR T cells are unable to induce a bystander effect, therefore treatment of solid tumors in which the targeted antigen is not expressed by all tumor cells will likely be unsuccessful. Secondly, however, combination strategies where the effects of CAR T cell therapy are augmented can be explored for tumor eradication. Our study suggests that the use of CTX or blockade of intratumoral Tregs are two such potential strategies.

Keywords: CAR T; epitope spreading; bystander effect; tumor antigen heterogeneity

MS05.05: Regional Delivery of CAR T Cells with Cell-intrinsic Checkpoint Blockade Eradicates Malignant Pleural Mesothelioma: Rationale for Clinical Trial

Linot C1, Quach H1, Adusumilli P1

1Memorial Sloan Kettering Cancer Center, New York, United States

Parallel Mini-Symposia 05: Cell Therapies and Mesothelin Directed Therapies, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Objectives: Malignant pleural mesothelioma (MPM) is a regionally aggressive malignancy with low PD-L1 expression and a low tumor mutational burden. Although checkpoint blockade (CPB) therapy has shown promising results in non-small cell lung cancer, results are not encouraging in MPM. Our laboratory ongoing clinical trial demonstrated the potential safety and anti-tumor efficacy of combining mesothelin-targeted chimeric antigen receptor (CAR) and anti-PD-1 CPB. Herein, we investigated whether CAR T-cell intrinsic CPB with PD1 dominant negative receptor (DNR) can be effective for clinical translation.

Methods: Human T-cells transduced with CD28 costimulated mesothelin-targeted CAR T cells (M28z) with PD1DNR were investigated against mesothelin-expressing cancer cells. In vitro, efficacy was evaluated with a chromium-51 release assay. T cell cytokine production was determined using Luminex multiplex assays. In vivo, tumor burden regression kinetics and median survival were determined by bioluminescence in a clinically-relevant orthotopic MPM model.

Results: MSLN PD1-DNR CAR T-cells exhibit robust antigen-specific cytotoxic activity, effector cytokine secretion against MPM cells at multiple E:T (effector to target) ratios. In vivo studies demonstrated that one single dose of intrapleural M28zPD1DNR CAR T-cells are able to eradicate the tumor and prolong survival (median survival 60 days) of mice compared to same dose of M28z CAR T cells (27.5 days)(see figure). CAR T-cell therapy combined with extrinsic PD1 blockade or intrinsic PD1DNR demonstrated similar anti-tumor efficacy with no toxicities. The differences in both strategies are highlighted in the table.

Conclusion: Our results demonstrate that regional administration of mesothelin-targeted CAR T-cell-intrinsic PD1DNR potentiate the efficacy of MSLN targeted CAR T-cell for MPM. These findings provide the rational for upcoming MSLN PD1DNR CAR T-cell clinical trial in 2020.

Keywords: Immunotherapy, CAR T cell, Mesothelin, PD-1 DNR
MS05.06: Examining the Interaction of Mesothelin and CA125 in Malignant Pleural Mesothelioma

Nash A1, Rouse E1, Robinson B1,3, Creaney J1,3
1National Centre of Asbestos Related Disease, Perth, Australia, 2University of Western Australia, School of Biomedical Science, Perth, Australia, 3Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Australia

Parallel Mini-Symposia 05: Cell Therapies and Mesothelin Directed Therapies, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Objective: The glycoprotein mesothelin is a clinical biomarker for MPM that is associated with increased tumour burden and decreased survival through a currently unknown mechanism. Cancer Antigen 125 (CA125) is an ovarian cancer biomarker that acts as a high affinity binding partner for mesothelin and can be co-expressed with mesothelin on MPM cells. Mesothelin-CA125 binding has been suggested to facilitate metastasis, and aggressive characteristics mediated by mesothelin have been demonstrated to be abolished by mutations removing the CA125 binding site on mesothelin. Our objective was to determine whether the binding of CA125 to cell surface mesothelin drives MPM progression. We hypothesised that CA125 binding to cell surface mesothelin would increase proliferation, metabolic activity, migration, chemoresistance and cell adhesion, characteristics that are implicated as mechanisms for mesothelin-driven cancer progression.

Methods: 12 cell lines derived from patient pleural effusion were used for in vitro testing, and cell lines were characterised according to CA125 and mesothelin expression using flow cytometry and enzyme-linked immunosorbent assay. The effect of exogenous CA125 or mesothelin treatment on MPM cell characteristics was determined using a variety of tests. Cell proliferation and metabolic activity were determined using live-cell imaging and MTT assay respectively, while cell migration was determined using scratch-wound assay. Cisplatin-induced cytotoxicity/apoptosis was measured in both cell spheroid and cell monolayer models to determine chemoresistance. Cell adhesion was assessed by monitoring cell cluster formation in low-adherence conditions.

Results: Of the cell lines used, 10/12 (83%) were characterised as mesothelin positive and 4/12 (33%) were CA125 positive, with 2/12 (17%) co-expressing both proteins. Use of live-cell imaging demonstrated that treating cells with soluble CA125 did not induce a significant change in proliferation, metabolic activity or mesothelin expression compared to untreated controls. However, CA125 treatment increased cisplatin-induced apoptosis for some cell lines in both cell monolayer and spheroid models. Treatment with soluble mesothelin increased cell migration, and reduced cisplatin-induced apoptosis in both cell monolayer and spheroid models, but did not affect proliferation or metabolic activity. Cultivation of cells under low-adherence conditions demonstrated that only mesothelin-positive cells formed cell clusters, regardless of CA125 expression.

Conclusion: Our findings suggest that CA125 binding to mesothelin does not regulate MPM progression. However, soluble mesothelin is likely to drive MPM progression by increasing chemoresistance and migration/invasion. We suspect that soluble mesothelin mediates aggressive cell characteristics by binding to cell surface CA125 or another unknown receptor, and that mesothelin expressed on the cell surface facilitates invasion by independently regulating cell-cell adhesion.

Mesothelin, CA125, MUC16, Mesothelioma

MS05.07: Engineering Chimeric Antigen Receptor T Cells to Secrete Fucosyltransferase Augments Cutaneous Lymphocyte Antigen Expression and Infiltration into Mesothelin Positive Tumors

Moon E1, Martinez M1, Kim S1, Lian L1, Sun J1, Leibowitz M, Albelda S1
1University Of Pennsylvania, Philadelphia, United States

Parallel Mini-Symposia 05: Cell Therapies and Mesothelin Directed Therapies, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Objectives: MPM survival positively correlates with the degree of tumor infiltrating lymphocytes (TILs). However, successful infiltration of T cells into tumor is a significant hurdle for immunotherapy in solid tumors like MPM. T cells
infiltrate tumors in three steps: 1) rolling along endothelium, 2) firmly adhering to endothelial cells, and 3) transmigrating in between endothelial cells. This process relies on the binding of T cells to P- and E-selectins on endothelial cells. P-selectin glycoprotein ligand-1 (PSGL1) (expressed on activated T cells) binds to P-selectin. PSGL1 undergoes posttranslational modification to become cutaneous lymphocyte antigen (CLA) which binds to E-selectin. This is carried out by fucosyltransferase VII (Fut7). We tested the hypothesis that engineering chimeric antigen receptor (CAR) T cells to secrete Fut7 would augment CLA expression and infiltration into mesothelioma tumors.

**Methods:** In-vitro: Human bulk T cells acquired from healthy donors through the Penn Human Immunology Core were activated in-vitro with anti-CD3/CD28 microbeads and transduced with high titer 3rd-generation lentivirus encoding for either SS1BBz (2nd generation mesothelin CAR signaling through 41BB and CD3z) or SS1BBz/Fut7. Fut7 transduction was confirmed via western blotting. CAR and CLA expression were measured via flow cytometry. SS1BBz and SS1BBz/Fut7 T cells were incubated with TNFa-exposed human umbilical vein endothelial cells (HUVECs; TNFa exposure to upregulate E-selectin) on a rocker and relative frequencies of T cells adhered to HUVECs was measured 30 minutes later. In-vivo: A squamous cell cancer cell line (SCC15) known to form discrete tumor nests in-vivo was transduced with lentivirus to stably express high levels of mesothelin (SCC15-meso) Immunodeficient, (NSG) mice were injected subcutaneously with 5 million SCC15-meso tumor cells. Once flank tumors established and grew to about 150mm3 in volume, mice were randomly assigned to one of three treatment groups: 1) Intravenous (IV) saline injection 2) 10 million SS1BBz CAR T cells IV x 1 3) 10 million SS1BBz/Fut7 T cells IV x 1

Five days after treatment initiation mice were sacrificed and tumors were harvested, digested, processed into single cell suspension and subjected to flow cytometry. A portion of the tumors were submitted for immunohistochemistry.

**Results:** In-vitro: SS1BBz and SS1BBz/Fut7. After 30 minutes of rocking incubation of T cells with TNFa-exposed HUVEC cells, twice as many SS1BBz/Fut7 T cells had adhered to HUVECs as SS1BBz T cells. In-vivo: Five days after starting treatments of SCC15-meso flank tumor engrafted mice, there were 5x as many T cells inside the flank tumors in the SS1BBz/Fut7 T cell mice as compared to the SS1BBz T cell mice (p<0.01) (Fig. 1a) IHC demonstrated greater CD8 staining in SS1BBz/Fut7 T cell treated mice vs. SS1BBz T cell treated mice. (Fig. 1b) SS1BBz/Fut7 TILs were all CLA positive whereas SS1BBz TILs were about 35% CLA positive.

**Conclusion:** Engineering T cells with Fut7 leads to enhanced expression of CLA. SS1BBz/Fut7 T cells demonstrate significantly greater adherence to E-selectin expressing HUVECs. Five days after adoptive transfer into NSG mice bearing well-established mesothelin-positive flank tumors, there is significantly greater infiltration of SS1BBz/Fut7 T cells compared to SS1BBz T cells.
MS06.04: Post-traumatic Stress as Asbestos Victim among Bereaved of Patients with Malignant Pleural Mesothelioma in Japan

Nagamatsu S1

1St. Luke’s International University, Tokyo, Japan

Parallel Mini-Symposia 06: Nursing and Supportive Care, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Objectives: This study is a part of a larger study about the quality of life of bereaved of patients died by MPM and aims to reveal the needs support of bereaved regarding the post-traumatic stress by qualitatively analyzing the open-ended comment form.

Methods: The original questionnaires were distributed to the bereaved of MPM through the patient advocacy groups, completed, and sent back to the researchers by postal mail. The answers of the open-ended comment form was analyzed qualitatively. The description relating to the PTSD symptoms in accordance with the DSM-IV-TR Criteria for PTSD (American Psychiatric Association) were collected. The St. Luke’s International University Research Ethics Committee approved this study (approval no. 16-A035).

Results: In total, 75 questionnaires were collected. 83% of patients were male and mean age on diagnosis was 67 years old and mean survival was 18 months. About bereaved, 79% were female and 73% were spouse and mean age of 63 years old and. The mean of bereavement time was 45 months.

Among 75 bereaved, 21 (28%) wrote answers which indicated post traumatic distress.

The narrative of the bereaved were shown in italics.

Insomnia: ‘I am in a darkness listening to the clock ticks.

Experiencing: ‘His voice is echoing saying “I do not want to die by mesothelioma.” I am so sorry for him.’

Avoidance: ‘I do not want to see the couples traveling together. It is too painful.’

Anger: ‘I am very angry against our country and company used asbestos. I hate asbestos. Why people do not care this social crime?’

Loss of interest: ‘Nothing interest me. I live for nothing now.’


Hypervigilance: ‘My father died by mesothelioma, I feel like I will die by mesothelioma too. My son will too. How can I tell my son this?’

Discussion: Bereaved of MPM experienced post-traumatic stress as asbestos victim. Our study showed that loosing loved one by MPM is not a natural bereavement but a traumatic event. It is recommended to research further to develop the psychological support on the bereaved of MPM.

Conclusions: Bereaved of MPM need support since death of family by MPM cause post-traumatic stress as asbestos victims.

mesothelioma, nursing, PTSD

MS06.05: Patient and Informal Carers Experience of Living With Mesothelioma: A Systematic Rapid Review and Synthesis of the Literature

Ejegi-Memeh S1, Sherborne V1, Harrison M1, Taylor B1, Tod A1, Gardiner C1

1Division of Nursing and Midwifery, Sheffield, United Kingdom

Parallel Mini-Symposia 06: Nursing and Supportive Care, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Objectives: In order to effectively provide support and care for individuals and families living with mesothelioma, we need to understand their experiences and priorities. This evidence review draws together existing research on the experience of people living with mesothelioma. The purpose of this review was to identify what is known about the experience of people living with mesothelioma, from the perspective of patients and their carers.

Methods: Review protocol registered on PROSPERO (CRD42020204726). Systematic searches were conducted across Medline, PsycInfo, Scopus and the Cumulative...
Index to Nursing and Allied Health Literature. Google Scholar was also searched. The inclusion criteria stipulated that studies were peer-reviewed, reported on the experience of living with mesothelioma from the perspective of patients and informal carers, were written in English, and were published between December 2008 and October 2020. The quality of the included studies was assessed using the Mixed-Methods Appraisal Tool. Data were extracted and a narrative synthesis developed.

Results: Twenty-five studies were identified that met the inclusion criteria. Twelve of the studies utilized qualitative methods, 12 utilized quantitative methods and one used mixed-methods.

Findings were divided into eight areas: experience of diagnosis; physical impact of mesothelioma; psychological impact of mesothelioma; impact on informal carers, carers and relationships; self-management; health care professionals and systems; treatment and trials; and asbestos exposure and compensation.

In addition to literature focusing on the devastating physical and psychological impact of a diagnosis of mesothelioma, there is a growing body of evidence showing that quality of life and well-being in a broader sense are also impacted by a diagnosis of mesothelioma.

Complex emotions regarding exposure to asbestos were reported. Not only anger and a sense of injustice, but also guilt and responsibility for potentially having exposed their family members to asbestos. The experiences of informal carers are increasingly being recognised as important. However, little research focused on the experiences of carers.

Professionals that were compassionate, honest and supportive positively influenced patient experience. Continuity, coordinated care and good communication between treatment centres were reported as important in the literature. Specialist nurses and good GP support were key to coordinated and individualised care. Non-healthcare professionals such as Asbestos Support Groups and legal professionals were also reported as valuable sources of support.

Challenges relating to trial participation included difficulties in assimilating information about the trial process, and understanding of randomisation and clinical equipoise. Motivations for taking part in trials included wanting to exhaust all treatment options, the possibility of enhanced care, and altruism. Travel time to trial centres, expenses for travel, and accommodation were reported as barriers to trial participation.

Conclusion: Over the past 12 years the volume of mesothelioma patient and carer experience research has grown. This has contributed to our understanding of the complex needs and experiences of mesothelioma patients and their carers. However, this review has identified several gaps in current evidence. Recommendations for further research are provided. The findings from the current review will inform a research prioritisation exercise that is being conducted by the Mesothelioma UK Research Centre in 2021.

Patient experience, informal carer experience, literature review

**MS06.06: Development of Mesothelioma Care Passport**

**Guerin M^1,2, Bolton S^2, Forde F^2**

^1 Liverpool University Hospitals, Liverpool, United Kingdom, ^2 Mesothelioma UK, Leicester, United Kingdom

**Parallel Mini-Symposia 06: Nursing and Supportive Care, Virtual, May 8, 2021, 12:30 AM - 2:00 AM**

**Objectives:** There is anecdotal evidence that cancer patients and carers experience difficulties navigating treatment and support. This is especially true when attending multiple sites and liaising with numerous health care professionals. Complex pathways can impact on the delivery of consistent and accurate information regarding treatment plans and care.

People suffering from Mesothelioma can have many complex health care needs, often requiring input from an array of service providers. Several studies document the considerable number of professionals that patients with cancer may encounter (1,2) ranging from local district general hospital, community services, local treatment centres, national clinical trial centres and hospices at varying stages throughout their pathway. When care is provided by multiple different professional’s gaps can occur, along with delays in transfer of records with informal communication often proving inconsistent alongside incomplete information around specialist intervention.

**MS06.06: Development of Mesothelioma Care Passport**

**Guerin M^1,2, Bolton S^2, Forde F^2**

^1 Liverpool University Hospitals, Liverpool, United Kingdom, ^2 Mesothelioma UK, Leicester, United Kingdom

**Parallel Mini-Symposia 06: Nursing and Supportive Care, Virtual, May 8, 2021, 12:30 AM - 2:00 AM**

**Objectives:** There is anecdotal evidence that cancer patients and carers experience difficulties navigating treatment and support. This is especially true when attending multiple sites and liaising with numerous health care professionals. Complex pathways can impact on the delivery of consistent and accurate information regarding treatment plans and care.

People suffering from Mesothelioma can have many complex health care needs, often requiring input from an array of service providers. Several studies document the considerable number of professionals that patients with cancer may encounter (1,2) ranging from local district general hospital, community services, local treatment centres, national clinical trial centres and hospices at varying stages throughout their pathway. When care is provided by multiple different professional’s gaps can occur, along with delays in transfer of records with informal communication often proving inconsistent alongside incomplete information around specialist intervention.
The overall aim of this development is to improve the mesothelioma patient experience by devising and evaluating a personalised patient held record. Promoting consistency and streamlining the pathway, eliminating delays in transfer of information, ensuring the patient is fully informed of treatment plans and decisions along with rationale for same.

Reports have shown that patients value hand held records as aide memoires. Studies have identified that having such tools are perceived to be beneficial, facilitating the sharing of important information thus averting the dependence of patients and families in difficult circumstances (3).

The development aims to minimize the distress caused by patients and carers when attending variable clinical setting ensuring smooth effective pathway. It also aims to provide the patients with ownership, assisting in preparation for meetings and discussion with their health care worker at a time when they may often feel lost and bewildered.

**Methods:** Interest was generated from patient and carer discussions at UK Action Mesothelioma days. Scoping exercises with local mesothelioma patient support groups highlighted areas of concern in timeliness and accuracy of the transferring of information across health care providers and feeling of “loss of control and involvement in one’s own care”

The qualitative, co-production study group consisted of Mesothelioma UK CNS, patients, carers and representation from the Mesothelioma UK operations team.

Other relevant personal invited onto the group as deemed necessary throughout the project including external facilitation and design specialists.

**Results:** Data was collected from focus group discussion and consultation group interviews (consisting of questionnaire, patient satisfaction, patient stories and experience)

All elements were subsequently reviewed by the group members with independent identification of main themes in order to develop relevant content.

**Conclusion:** The Mesothelioma passport will ensure the patient is fully informed of treatment plans and decisions whilst owning a written account of the rationale for such decisions.

Development of a patient focused national tool will aide patient self-management in mesothelioma care. Future evaluations of the tool will determine the effectiveness of the project collecting the views of service users around the acceptability of the tool

(1) Smith Palliative medicine 1999;  
(2) Jarrett Journal of advanced nursing 1999;  
(3) Williams Quality in health care 2001

**Keywords:** Patient information, Mesothelioma Passport
**MS06.07: The Impact of the COVID-19 Pandemic on the Experiences of People With Mesothelioma and Their Informal Carers in the UK: Recommendations for Practice**

Taylor B\(^1\), Tod A\(^1\), Gardiner C\(^1\), Forde F\(^2\), Creech L\(^2\), Darlison L\(^2\)

\(^1\)University of Sheffield, Sheffield, United Kingdom, \(^2\)Mesothelioma UK, Leicester, United Kingdom

**Parallel Mini-Symposia 06: Nursing and Supportive Care, Virtual, May 8, 2021, 12:30 AM - 2:00 AM**

**Objectives:** The burden and impact of covid-19 on health care systems worldwide carries significant implications for cancer patients across the care pathway. Accessing diagnostic services, timely treatment and monitoring disease progression is vital for mesothelioma patients, approximately 60% of whom do not survive the disease for beyond 12 months (RCP, 2020). The UK has the highest incidence of mesothelioma globally with approximately 2,700 people diagnosed annually (CRUK, 2020). Mesothelioma UK (MUK), an independent national charity, conducted two national surveys. They aimed to capture the impact of the pandemic on mesothelioma patients and carers in the UK. Findings presented here focus on the impact of covid-19 on patients and informal carers. Implications for practice are considered.

**Methods:** MUK conducted two surveys; one with mesothelioma patients and carers in April 2020 and the second with Mesothelioma UK Clinical Nurse Specialists (MCNSs) in August 2020. The patient and carer survey was developed by senior nurses and reviewed by patient representatives. A convenience sample was recruited via the MUK website, social media platforms and support groups. MUK then designed a second survey and invited email responses from the 28 MCNSs working across the UK. Both surveys comprised a mix of open and closed questions with space for additional comments. Questions with closed responses were collated and analysed using descriptive statistics in Excel. Free text responses were analysed using the principles of thematic analysis. Themes and sub-themes were tabulated and areas of overlap between the two surveys were identified.

**Results:** Responses were received from 35 patients, 29 carers, and 20 MCNSs. The findings suggest that mesothelioma patients and their carers have been severely affected by the impact of the covid-19 pandemic. The burden of covid-19 has necessitated changes to the provision of and access to health services, care and advice. For mesothelioma patients these changes have caused disruption to treatment schedules and CT scans, difficulties communicating remotely with health care teams, confusion about vulnerability to covid-19 and social distancing measures. Mesothelioma patients and their carers have also experienced considerable emotional and psychological burden as a result of isolation, fear of catching covid-19 and feeling unworthy of adequate treatment and care. These study findings have informed the development of practice recommendations, outlining ways in which health care professionals and support organisations can improve the experiences of mesothelioma patients and carers during the remainder of this pandemic.

**Conclusion:** Covid-19 presents an ongoing risk that will shape clinical practice for the foreseeable future. These findings provide unique evidence-based insights into the experiences of mesothelioma patients and their carers during the covid-19 pandemic. The findings suggest that mesothelioma patients have been disproportionately affected. Planning is required to ensure people with mesothelioma receive the best possible support and treatment during the remainder of the covid-19 pandemic, and avoidable negative consequences of the pandemic are avoided.


Patient and carer experience Covid-19 impact
**MS07.01: Assessment of Potential Predictors of Calretinin and Mesothelin Plasma Levels To Improve the Diagnostic Performance To Detect Malignant Mesothelioma**


1Institute For Prevention And Occupational Medicine Of The German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany, 2Institute of Medical Informatics, Biometry and Epidemiology, University Duisburg-Essen, Essen, Germany

**Parallel Mini-Symposia 07: Recent Developments: Genetics and Biomarkers, Virtual, May 8, 2021, 12:30 AM - 2:00 AM**

**Objectives:** Calretinin and mesothelin are two promising blood-based biomarkers for the detection of malignant mesothelioma at early stages. The objective of this study was to identify factors influencing calretinin and mesothelin concentrations in plasma of cancer-free men in order to minimize false-positive tests using commercial assays in clinical routine.

**Methods:** The present analyses used data and blood samples of 569 cancer-free men of the population-based Heinz Nixdorf Recall Study (HNRS) in Germany. Information on socio-demographic characteristics, current and chronic diseases, as well as medications was derived from questionnaires. We further included follow-up information on the development of cancer and data on 36 blood parameters. Calretinin plasma concentration was assessed using the Calretinin ELISA kit (enzyme-linked immunosorbent assay; DLD Diagnostika GmbH, Germany). Mesothelin plasma concentration was determined using the Mesomark ELISA kit (Fujirebio Diagnostics Inc., USA) and the CLEIA (chemiluminescent enzyme immunoassay) Lumipulse G Mesothelin (Fujirebio Inc., Japan). Median and inter-quartile range (IQR) were used to depict the distribution of marker concentrations. Prevalence odds ratios (POR) and 95% confidence intervals (95% CIs) were calculated as effect estimate for marker concentrations being above their cut-offs.

**Results:** The median age of the 569 analyzed men was 70 years (range 56 – 84 years). Cancer other than mesothelioma was diagnosed in 20 men after blood collection. The most frequently self-reported diseases were hypertension (64.1%) and diabetes mellitus (21.1%). The median calretinin concentration was 0.17 ng/mL (IQR 0.12 ng/mL – 0.24 ng/mL) and showed nine false-positive tests (specificity 98.4%, 95% CI 97.0% - 99.2%). Median mesothelin concentrations were 0.66 nM (IQR 0.49 nM – 0.94 nM) and 0.84 nM (IQR 0.57 nM – 1.21 nM) using the CLEIA and ELISA, respectively. In both mesothelin assays, false-positive tests were observed for 24 subjects (specificity 95.8%, 95% CI 93.8% – 97.2%). The concentrations of calretinin and mesothelin increased by age and by cystatin C (reflecting renal dysfunction). Elevated cystatin C was a major predictor of elevated marker concentrations (calretinin: POR=17.5, 95% CI 4.40 – 69.7; mesothelin CLEIA: POR=12.1, 95% CI 4.46 – 33.0; mesothelin ELISA: POR=9.58, 95% CI 3.46 – 26.5). Mesothelin was additionally affected by bronchitis. Furthermore, elevated C-reactive protein and current hypertension affected the mesothelin concentration determined by ELISA.

**Conclusions:** The commercially available assays for calretinin and mesothelin approved for clinical diagnostics showed high specificities in the population-based cohort of elderly men. High specificities of calretinin and mesothelin were based on small numbers of false-positive tests limiting the power of detecting predictors. However, this evaluation provides a basis to consider influencing factors in order to further improve the diagnostic procedure in clinical routine.

biomarker, epidemiology, renal dysfunction, hypertension

**MS07.02: Biallelic Inactivation of Tumor Suppressor Genes in Mesothelioma Involving Balanced Translocations**


**Abstract:**

**Results:** The median age of the 569 analyzed men was 70 years (range 56 – 84 years). Cancer other than mesothelioma was diagnosed in 20 men after blood collection. The most frequently self-reported diseases were hypertension (64.1%) and diabetes mellitus (21.1%). The median calretinin concentration was 0.17 ng/mL (IQR 0.12 ng/mL – 0.24 ng/mL) and showed nine false-positive tests (specificity 98.4%, 95% CI 97.0% - 99.2%). Median mesothelin concentrations were 0.66 nM (IQR 0.49 nM – 0.94 nM) and 0.84 nM (IQR 0.57 nM – 1.21 nM) using the CLEIA and ELISA, respectively. In both mesothelin assays, false-positive tests were observed for 24 subjects (specificity 95.8%, 95% CI 93.8% – 97.2%). The concentrations of calretinin and mesothelin increased by age and by cystatin C (reflecting renal dysfunction). Elevated cystatin C was a major predictor of elevated marker concentrations (calretinin: POR=17.5, 95% CI 4.40 – 69.7; mesothelin CLEIA: POR=12.1, 95% CI 4.46 – 33.0; mesothelin ELISA: POR=9.58, 95% CI 3.46 – 26.5). Mesothelin was additionally affected by bronchitis. Furthermore, elevated C-reactive protein and current hypertension affected the mesothelin concentration determined by ELISA.

**Conclusions:** The commercially available assays for calretinin and mesothelin approved for clinical diagnostics showed high specificities in the population-based cohort of elderly men. High specificities of calretinin and mesothelin were based on small numbers of false-positive tests limiting the power of detecting predictors. However, this evaluation provides a basis to consider influencing factors in order to further improve the diagnostic procedure in clinical routine.

biomarker, epidemiology, renal dysfunction, hypertension
ABSTRACTS

Mayo Clinic, Rochester, United States, Netherlands Cancer Institute, Amsterdam, Netherlands

Parallel Mini-Symposia 07: Recent Developments: Genetics and Biomarkers, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Objectives: Genomic characterizations of mesothelioma have uncovered frequent inactivation of tumor suppressor genes like TP53, CDKN2A, BAP1, and NF2 due to copy number loss or mutation. Typically, methods such as chromosomal microarray, exome sequencing, and low pass whole genome sequencing have been used to determine loss of these genes. These methods miss specific genetic alterations, such as balanced translocations and can underestimate the prevalence of biallelic inactivation of these genes in cancer. We profiled mesothelioma samples using a large fragment whole genome sequencing technology called mate-pair sequencing (MPseq) which is designed to determine translocation breakpoint locations, including balanced translocations. With this approach we sought to determine whether balanced translocations is a mechanism of biallelic loss of tumor suppressor genes in mesothelioma.

Methods: The biopsy specimens from 42 patients with pleural mesothelioma were obtained just prior to receipt of second or later lines of immunotherapy. MPseq was used for genomic profiling. The resulting sequencing data was aligned using the mapping algorithm BIMA, which is specifically designed for use with MPseq. SVATools was used for structural variant detection and can identify copy number variants (CNVs) and translocations. Translocation breakpoint locations were combined with copy number information to determine cancer-related genes that were inactivated via balanced translocation.

Results: We found biallelic loss by a combination of copy number loss and balanced translocation of one or more of the common tumor suppressor genes (CDKN2A, BAP1, TP53, NF2) in eight of the 42 cases (19%). There were a total of 11 cases (26%) with the inactivation of a known COSMIC tumor suppressor gene (including the common ones listed above and FOXO1, SUFU, and PIK3C3) by a combination of copy number loss and a balanced translocation. Some of these other tumor suppressor genes have not been reportedly linked to mesothelioma previously. Five cases (12%) showed biallelic loss of NF2 via copy number loss with balanced translocation. Compared to all other genes, the biallelic inactivation of NF2 more commonly resulted from balanced translocations.

Conclusion: We found that while BAP1 and CDKN2A are predominantly inactivated via homozygous loss, TP53 and NF2 inactivation rarely involves large regions of homozygous loss. NF2 is particularly prone to inactivation via balanced translocation, suggesting that the prevalence of NF2 inactivation in mesothelioma may be underestimated with common sequencing approaches. More comprehensive or targeted genetic analysis may be needed to determine NF2 status at diagnosis.

NF2; Biallelic inactivation; Balanced translocations; Tumor suppressor genes

MS07.03: Calretinin and Mesothelin for the Early Detection of Mesothelioma – Results of the MoMar Cohort

Johnen G1, Raiko I1, Wichert K1, Pesch B1, Weber D1, Lehnert M1, Casjens S1, Hagemeyer O1, Taeger D1, Brüning T1, MoMar Study Group1

1Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany

Parallel Mini-Symposia 07: Recent Developments: Genetics and Biomarkers, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Background: The incidences of malignant mesothelioma (MM) and other asbestos-related occupational diseases remain high. Secondary prevention covers follow-up preventive health care of former asbestos workers aiming at the early detection of MM. An earlier diagnosis could improve options for current and future therapies. Biomarkers, which can easily be detected in body fluids, might be a promising approach. So far, many biomarker candidates have been identified and described using conventional case-control studies with cases mostly at later tumor stages. However, a marker validation with patients at early stages or with prediagnostic samples is difficult because the establishment of necessary prospective cohorts with serial prediagnostic samples is very time-consuming and costly.
Methods: For the MoMar cohort almost 2,800 patients with benign asbestos-related diseases (pleural plaques, rind or thickening, pleurisy, and/or asbestosis) were recruited between 2008 and 2018 who participated in repeated annual examinations resulting in over 12,500 blood samples. A follow-up of the MoMar cohort was conducted until 2019. During this time 43 cases of MM occurred. Using a nested case-control design, the cases were matched to 172 controls from the cohort (ratio 1:4). Concentrations of calretinin and mesothelin were determined in plasma samples using commercial ELISA (enzyme-linked immunosorbent assay) kits. Marker performance was determined by ROC (receiver operating characteristic) analysis.

Results: Looking at the time courses the marker concentrations in MM cases appear to increase mostly in the year before clinical diagnosis. The relevant time interval between $t=-13$ and $t=-0.7$ months before clinical diagnosis includes 32 cases. At a pre-set specificity of 98% the sensitivity of each individual marker was 34% for calretinin and 25% for mesothelin. When both markers were combined, the sensitivity increased to 44%.

Conclusion: Using a high-risk cohort of asbestos-exposed workers we were able, for the first time, to demonstrate the value of a biomarker combination to detect MM in prediagnostic plasma samples. A gain in time of up to a year could help to initiate treatment when tumors are at earlier stages and have not yet spread. The combination of calretinin and mesothelin improved the performance of the individual markers and thus implies at least a partial complementation. There is hope that additional markers might improve the sensitivity even further but it is important to maintain a high specificity to avoid unnecessary psychological distress for the patients by false-positive results. The MoMar cohort is open for collaborations to validate any promising new markers. A validation of the combination of calretinin and mesothelin in an independent cohort would also be desirable.

biomarker, prediagnostic plasma, early diagnosis, prospective cohort

MS07.04: Genomic and Transcriptomic Profiling of Malignant Mesothelioma Patients Identifies Gene Signatures Predictive of Survival and Response to Immuno and Chemotherapy


1Cancer Data Science Laboratory, National Cancer Institute, NIH, Bethesda, United States, 2Thoracic and GI Malignancies Branch, National Cancer Institute, NIH, Bethesda, United States, 3Genetics Branch, National Cancer Institute, NIH, Bethesda, United States, 4Samsung Medical Center, Sungkyunkwan University School of Medicine, Suwon, Republic of Korea

Parallel Mini-Symposia 07: Recent Developments: Genetics and Biomarkers, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Objectives: Malignant mesothelioma (MM) is an aggressive cancer with limited treatment options and poor prognosis. Malignant pleural mesothelioma comprises 80% of the cases and has worse outcome than malignant peritoneal mesothelioma. An in-depth knowledge of genetic, transcriptomic and immunogenic events involved in MM is critical for successful development of prognostics and therapeutic modalities. In this study we aim to address this by exploring a new large scale patient tumor dataset containing both pleural and peritoneal mesothelioma patient samples.

Methods: We performed whole-exome sequencing of germline and tumors of 122 patients with pleural (n=59), peritoneal (n=61) and tunica vaginalis (n=2) mesothelioma, and RNA-sequencing of 100 tumors to identify pathogenic variants, somatic mutational signatures, and prognostic gene expression signatures, predictive of patient survival and tumor response to therapies. We validated our findings using the TCGA and Bueno et al. mesothelioma datasets.

Results: The important findings from this study include:

a) Key somatic mutational signatures are associated with DNA repair pathways and BRCA1 associated protein-1 (BAP1) is the most commonly mutated gene (~13% with germline mutation).
b) Unlike previous studies which mainly focused on pleural mesothelioma patients, our dataset includes comparable number of patients of both pleural and peritoneal subtypes, and hence give us a better understanding of the similarities and differences that may exist in the molecular pathophysiology of the two anatomically distinct disease.

c) We identified a set of 48 genes, a “mesothelioma prognostic signature”, whose high expression level is associated with poor survival (Cox regression, FDR < 0.1). These genes are enriched for genes related to cell cycle and DNA repair. This signature is highly predictive of patient survival in two other independent, pleural mesothelioma cohorts: TCGA (Hazard ratio (HR) = 2.6, P = 6.94e-10) and Bueno et al. mesothelioma dataset (HR = 1.49, P = 4.34e-07), after controlling for age and gender.

d) Among the 48 genes, the expression of CCNB1 is highly predictive of patient survival suggesting its important role in MM, possibly via its involvement in the CDK1-CCNB1-CCNF complex (HR = 2.54, P = 1.89e-08 for TCGA; HR = 1.40, P = 1.65e-05 for Bueno et al. dataset).

e) Using a synthetic lethality (SL) based precision-oncology computational framework for analyzing the patients' transcriptomic data, we were able to accurately predict response to an anti-PD1 immune checkpoint inhibitor and combination therapies with pemetrexed (chemotherapy) in mesothelioma patients. The SL profiles successfully predicted the overall patient-response observed across targeted, immuno- and chemotherapies in 11 independent mesothelioma clinical trials (Spearman's ρ = 0.64, P = 0.0348). This is the first analysis shown to successfully predict overall patient-response for various treatments within a cancer type.

Conclusion: By analyzing the tumor genomic and transcriptomics data of a large cohort of MM patients, we identify gene expression prognostic markers predictive of patient survival and response to therapy, both as independent signatures and via their SL interactions. These findings lay a basis for the future development of personalized therapy approaches for mesothelioma patients.

mesothelioma, biomarkers, survival analysis, drug response, pleural, peritoneal

MS07.05: Importance of Cullin4 Ubiquitin Ligase in Malignant Pleural Mesothelioma

Meerang M1, Kreienbühl J¹, Orlowski V¹, Müller S¹, Kirschner M¹, Opitz I¹

¹Department of Thoracic Surgery, University Hospital Zürich, Zürich, Switzerland

Parallel Mini-Symposia 07: Recent Developments: Genetics and Biomarkers, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Background: Malignant pleural mesothelioma (MPM) is primarily driven by loss of tumor suppressor genes. In this study, we explored importance of cullin4 (CUL4; 2 paralogs, CUL4A and CUL4B), a member of the cullin protein family that have been shown to be dysregulated in MPM as a consequence of tumor suppressor gene NF2 loss. We also evaluated the efficacy of the cullin inhibition by pevonedistat, a small molecule inhibiting cullin neddylation.

Methods: We assessed the expression of CUL4A and CUL4B in tissues using immunohistochemistry (IHC) and quantitative real time PCR. We tested the efficacy of pevonedistat in 13 MPM cell lines in 2D and 3D culture compared to non-malignant mesothelial cells. Four groups of severe combined immunodeficiency SCID mice (n=8/group) bearing intraperitoneal (ip.) pevonedistat sensitive (MSTO211H) or resistant (ACC-Meso1) cell lines were treated with pevonedistat (50 mg/kg; ip.) on a 5day on/5day off schedule for 3 cycles. Treatment efficacy was assessed by means of overall survival. To evaluate the mechanism of treatment, additional groups of mice (n=5/group) were treated for one cycle followed by tissue collection and analysis.

Results: Gene expression of CUL4A and CUL4B were upregulated in MPM tumor specimens compared to non-malignant pleural tissues. Data from the TCGA MPM cohort revealed that high CUL4B gene expression was associated with short disease free survival. Accordingly, using IHC on tissue microarray, we demonstrated that high CUL4B protein expression was associated with short progression free survival of MPM patients. Five MPM cell lines (38%) were highly sensitive to cullin inhibition by pevonedistat (IC50<0.5 μM). This remained true in 3D spheroid culture. The treatment induced S/
G2 cell cycle arrest and accumulation of cells undergoing DNA rereplication (containing >4N DNA content) more predominantly in the sensitive cell lines. DNA rereplication is known to be mediated by CDT1 accumulation and indeed the accumulation of CDT1 was detected after the treatment. Nevertheless, there was no difference in the extent of CDT1 accumulation comparing between sensitive and resistant cell lines. In vivo, pevonedistat treatment significantly prolonged survival of mice bearing both sensitive (MSTO211H) and resistant (ACC-Meso-1) MPM tumors. Pevonedistat treatment reduced growth in pevonedistat sensitive tumor but increased apoptosis in pevonedistat resistant tumor. Thus, we analyzed cells associated with tumor microenvironment including mouse macrophage (F4/80+) and vessel formation (CD31+) that may explain the efficacy of pevonedistat in the resistant model. The treatment significantly reduced numbers of tumor associated macrophage in resistant tumors, while it showed no effect in sensitive tumors. The treatment did not alter polarization of macrophage as shown by no change in the expression of Arginase1, a marker of immunosuppressive M2 macrophage, after treatment. There was no effect on blood vessel formation in both tumor models at this time point.

Conclusion: High CUL4B expression may play a role in MPM progression. Inhibition of cullins by pevonedistat induced growth arrest and DNA re-replication in a subset of MPM. Pevonedistat showed favorable effect for MPM treatment in vivo, even for a resistant tumor model. This effect may be mediated by reduced tumor-associated macrophage infiltration.

Cullins, CUL4A, CUL4B, Pevonedistat, Neddylation, NF2, treatment target, tumor microenvironment

MS07.06: Inactivation of the BAP1 Tumour Suppressor in Mesothelioma Suppresses Expression of the 14q32.31 miRNA Locus, Contributing to the Cancer Phenotype

Butt Z1, Tripari M1, Barnett S1, Silva L1, Hammond D2, Kenyani J1, Herrmann A1, Kalirai H3, Sacco J3, Coulson J1
1Molecular Physiology & Cell Signalling, Institute of Systems, Molecular & Integrative Biology, University of Liverpool, Liverpool, UK, 2Biochemistry & Systems Biology, Institute of Systems, Molecular & Integrative Biology, University of Liverpool, Liverpool, UK, 3Molecular & Clinical Cancer Medicine, Institute of Systems, Molecular & Integrative Biology, University of Liverpool, Liverpool, UK

Objectives: BRCA-1 Associated Protein 1 (BAP1) is a nuclear deubiquitylating enzyme whose expression is frequently lost through somatic or germline mutation in malignant pleural mesothelioma (MPM). Molecular analysis of MPM by several groups has found dysregulated microRNA (miRNA) expression. BAP1 regulates mRNA transcription, but its direct importance in determining miRNA expression in mesothelioma is not well understood. We therefore set out to identify and investigate BAP1-dependent miRNA networks in mesothelioma that contribute to the cancer phenotype and may influence therapeutic strategies.

Methods: We gene-edited the BAP1 locus to produce isogenic MeT5A mesothelial cells deficient in BAP1. We utilised the NanoString nCounter human v3 miRNA expression assay to profile the miRNome in these cells and in a panel of patient-derived MPM cell lines (MesobanK and ATCC) stratified by BAP1 status. Data were interrogated by unsupervised hierarchical clustering and gene ontology term enrichment analysis, encompassing biological processes, cellular compartments or molecular functions. Pathway enrichment analysis was also performed. We used PaintOmics (http://www.paintomics.org/) to integrate multi-omics data sets for visualisation onto KEGG pathways. Input data sets were RNA-seq, proteomics and miRNA from isogenic MeT5A mesothelial cells. Expression of selected miRNAs and their target proteins are being evaluated by qRT-PCR and immunoblotting following siRNA depletion, HDAC inhibition, or miRNA manipulation.

Results: In total, we identified ~400 unique miRNAs in the isogenic MeT5A cell lines. Compared with parental cells, 113 miRNAs were significantly (p<0.05) modulated by >1.5-fold in BAP1-deficient cells, and these miRNAs impact upon numerous cancer-associated pathways. Gene ontology analysis of targets for BAP1-dependent miRNAs highlighted cellular processes already associated with BAP1 (G1/S progression, glucose metabolism, cell
migration) and novel pathways (p53 signalling and the PRC1 complex), whilst PaintOmics analysis showed enrichment for glutathione and pyrimidine metabolism pathways. Most strikingly associated with BAP1-status was silencing of the miRNA cluster encoded by the chromosome 14q32.31 tumour suppressor locus in BAP1-deficient MeT5A. 14q32.31 miRNAs were particularly enriched for cancer-associated pathways, such as p53 signalling and transcriptional misregulation in cancer. Silencing of selected 14q32.31 miRNAs was further validated by qRT-PCR. We found that these 14q32.31 miRNAs are also silenced in a subset of BAP1-altered epithelioid MPM cell lines that additionally display elevated HDAC4 expression. Importantly, preliminary experiments suggest that 14q32.31 miRNAs such as miR-127-3p are de-repressed by HDAC4 depletion.

Conclusion: By employing an isogenic cell model, our study showed that BAP1 loss can reprogram miRNA expression in mesothelioma. BAP1 deficiency alone resulted in the silencing of a tumour-suppressive miRNA cluster mapping to chromosome 14q32.31 and whose clinical relevance was confirmed in a subset of BAP1-altered epithelioid MPM cell lines. Preliminary experiments suggest that 14q32.31 miRNAs are silenced in a subset of BAP1-altered epithelioid MPM cell lines that additionally display elevated HDAC4 expression. Importantly, preliminary experiments suggest that 14q32.31 miRNAs such as miR-127-3p are de-repressed by HDAC4 depletion.

**MS07.07: Optimizing Survival Prediction in Malignant Mesothelioma; Development and External Validation of A Clinical Prediction Model (MESOPRO)**

de Gooijer C\(^1\), Buikhuisen W\(^1\), van der Noort V\(^1\), Disselhorst M\(^2\), Quispel-Janssen J\(^3\), Schunselaar L\(^4\), Baas P\(^1\), van den Broek D\(^1\), Stuiver M\(^1\), Scherpereel A\(^5\), Fennell D\(^6\), Creaney J\(^7\), Nowak A\(^7\), Burgers J\(^1\)

\(^1\)Netherlands Cancer Institute, Amsterdam, Netherlands, \(^2\)Noordwest Ziekenhuisgroep, Alkmaar, Netherlands, \(^3\)Haaglanden Medical Center, ’s-Gravenhage, Netherlands, \(^4\)Leiden University Medical Center, Leiden, Netherlands, \(^5\)Hospital of the University (CHU) of Lille, Lille, France, \(^6\)University of Leicester, Leicester, Great Britain, \(^7\)University of Western Australia, Perth, Australia

Parallel Mini-Symposia 07: Recent Developments: Genetics and Biomarkers, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

**Objectives:** Prognosis of malignant mesothelioma (MM) displays a wide range. Treatment consists mostly of palliative systemic therapy. Several prognostic clinical prediction model models (CPM’s) have been established in the past. However, accuracy is limited for individual prediction. We developed, and will validate a prognostic CPM –MESOPRO- for MM patients who are about to start any new systemic therapy.

**Methods:** This multi-cohort study consisted of a four-step approach of model derivation, internal-, narrow- and broad validation. We created a Cox proportional hazard model for overall survival, using a landmark approach (every start of a new systemic therapy defined as landmark). The pooled dataset consisted of a consecutive cohort of MM patients who received systemic treatment in the Netherlands Cancer Institute (Jan. 2014- July 2020) and 5 Dutch MM trials (NVALT5, NVALT19, NivoMes, INITIATE, N08CPA). The set was randomly split in two cohorts for model derivation and internal validation (n=700) and narrow-validation (n= 176). Three international independent cohorts of MM patients, which started systemic therapy, will be used for broad validation. Furthermore, we will develop and validate imputation models to handle real-time missing predictors.

**Results:** Out of 16 candidate predictors, the following 10 variables seemed to add to the prognostication: gender, location (peritoneal vs pleural), pathological subtype (epithelial vs non-epithelial), WHO performance score (0 vs 1 and 1 vs 2-3), CYFRA 21.1, hemoglobin, thrombocytes, alkaline phosphatase and albumin. The C statistic was 0.71, allowing a clear discrimination between
ABSTRACTS

3 or 4 prognostic subsets of patients. Data regarding narrow- and broad validation will be presented at the iMiG conference 2021.

**Conclusion:** To our knowledge, the MESOPRO score is the first CPM developed for patients with MM who start a systemic therapy. Our CPM outperformed the EORTC prognostic test from 1998 in our derivation cohort, possibly because individual predictors were incorporated as continuous variables, serum Cyfra 21.1 plasma levels were added, and more appropriate statistical tools were available. Once validated, we plan to construct an online tool, supporting individual patients and their physicians in clinical decision making.

**MS07.08: Blood and FBLN3: Be Careful How and What You Collect**


1NYU Langone Medical Center, New York, United States, 2SUNY Upstate Medical University, Syracuse, USA, 3University of Pennsylvania Medical Center, Philadelphia, USA, 4University of Hawaii Medical School, Honolulu, USA, 5Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany

**Parallel Mini-Symposia 07: Recent Developments: Genetics and Biomarkers, Virtual, May 8, 2021, 12:30 AM - 2:00 AM**

**Objectives:** Fibulin 3 is a controversial diagnostic blood based biomarker for mesothelioma (MPM) with validations in North America, Turkey, China, and Egypt, and failures in Europe, UK, and Australia. The lack of proper ELISAs has been partly blamed, along with suspicion of cohort impropriety; however, a prognostic signal in pleural fluid has been validated in the US, Australia, and Europe. We present a blinded analysis from UPenn which validated FBLN3; however, FBLN3 once again failed in a blood-based study investigating Calretinin and FBLN3 with mutual exchange of blinded specimens. The possible reasons for the FBLN3 9 year controversy were investigated.

**Methods:** Three studies are reported. UPENN validation: From the NIEHS SRP grant, blinded samples of plasma from 34 pretreatment MPMs with 27 matched postoperative plasmas along with 34 individuals with documented asbestos exposure had FBLN3 quantification using a novel NYU-constructed ELISA using mAB428.2. Calretinin-FBLN3 Exchange Study: blinded plasma samples from 120 MPMs, 50 asbestos exposed (AE) individuals, and 30 individuals with non-MPM effusions were sent to German investigators for Calretinin determination. In turn, NYU received blinded plasma samples from MPM patients and 75 AE individuals for mAB428.2 ELISA. Analyses were performed via ROC curves. Vehicle comparison experiment: 60 cc of fresh blood from a “normal” volunteer was divided into a 30 cc aliquot with recombinant FBLN3 spiked in for a concentration of 600ng/ml and a 30 cc aliquot without spike in. Each of these aliquots were then drawn into either a K2 monovette with polypropylene gel (Germany), K2 EDTA polypropylene spray, or K3EDTA liquid in glass tubes. These tubes were then immediately processed in an identical fashion for subsequent FBLN3 determination. Non-reducing western gels were performed on all samples with positive control lanes of recombinant FBLN3.

**Results:** Figure 1a ROC reveals an AUC of 0.97 for the NYU plasma cohort of 129 MPMs compared to that of 172 AE and 172 non-MPM effusions. Blinded validation with UPENN revealed an AUC of 0.89. The NYU cohort samples sent to Germany validated the Calretinin assay (matching fibulins for those samples are seen in Figure 4D). As seen in Figure 1F, the FBN3 assay failed with German samples that worked perfectly for the Calretinin assay. Since blood collection methods were different between Germany and US, the vehicle comparison experiment (Figure 2d) was performed, and the results seen in Table 1. While K3 glass revealed “normal” FBLN3 levels for the non spike-in and expected spike-in levels, the German-used monovette and the universal K2 tube levels were non sensical. Western blots of selected German samples were characterized by either di-trimers or degradation (Figure 2B,2C), not seen in the K3 glass NYU study (Figure 2A). Western blot of the vehicle comparison plasmas revealed expected bands with K3, while K2 spray and monovette samples were degraded. Of note, 50 NYU matched serum and plasma FBLN3 levels correlated (r=0.9329, p<0.0001)

**Conclusions:** FBLN3 collection will influence ELISA determinations and must be standardized. Serum levels may be the most convenient and accurate to insure concordance between geographic sites.
ABSTRACTS
ABSTRACTS
MS07.09: Malignant Pleural Mesothelioma: Germline Variants May Steer Tailored Treatment

Sculco M1, La Vecchia M1, Aspesi A1, Clavenna M1, Casalone E2, Allione A2, Grosso F3, Libener R4, Muzio A5, Rena O6, Parini S6, Baietto G6, Boldorini R7, Migliore E8, Mirabelli D9,10, Magnani C10, Ferrante D10, Matullo G2,9,11, Dianzani I1,10,

1Department of Health Sciences, Università del Piemonte Orientale, Novara, Italy, 2 Department of Medical Sciences, Università di Torino, Torino, Italy, 3Mesothelioma Unit, AO SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, 4Pathology Unit, AO SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, 5Division of Medical Oncology, Ospedale Santo Spirito, Casale Monferrato (Alessandria), Italy, 6Thoracic Surgery Unit, AOU Maggiore della Carità, Novara, Italy, 7Department of Health Sciences, Section of Pathological Anatomy, Università del Piemonte Orientale, Novara, Italy, 8Unit of Cancer Epidemiology, CPO-Piemonte and Università di Torino, , Italy, 9Interdepartmental Center for Studies on Asbestos and other Toxic Particulates “G. Scansetti”, Università di Torino, , Italy, 10Department of Translational Medicine, Unit of Medical Statistics, Università del Piemonte Orientale and Cancer Epidemiology, CPO Piemonte, Novara, Italy, 11Medical Genetics Unit, AOU Città della Salute e della Scienza di Torino, Italy

Parallel Mini-Symposia 07: Recent Developments: Genetics and Biomarkers, Virtual, May 8, 2021, 12:30 AM - 2:00 AM

Objectives: A direct correlation between the amount of asbestos exposure and the risk of malignant pleural mesothelioma (MPM) is apparent, but only a small proportion (10-17%) of the individuals exposed to high levels of asbestos develop MPM. This observation and the report of families with multiple MPM cases suggest a role for inherited predisposition. The BAP1 gene is responsible for an inherited cancer syndrome that includes MPM in its cancer constellation. Among patients with familial MPM, the prevalence of germline mutations in BAP1 gene is 6-7%. We and others have identified that 10% of patients with malignant mesothelioma carried germline mutations in genes involved in DNA repair pathway. The most represented DNA repair pathway is homologous recombination repair (HRR), a pathway expected to correct the DNA breaks caused by asbestos fibers. We showed that patients carrying a germline mutation in DNA repair genes were exposed to a lower amount of asbestos compared to non-mutated patients, suggesting that they were more sensitive to asbestos and implying a gene/environment interaction. We aimed to confirm the prevalence of pathogenic mutations in HRR genes in a large panel of patients with MPM.

Methods: We screened for germline mutation 107 cancer-predisposing genes in 113 MPM patients by next generation sequencing (NGS). A further patient was recruited for diagnostic purposes because of a peculiar family history of mesothelioma and analyzed by Sanger sequencing of BAP1. Asbestos exposure was quantified in 113 patients. We applied stringent criteria to include only pathogenic variants (PVs): i) a minor allele frequency (MAF) of less than 0.01 in the ExAC browser and 1000 Genomes for the European population and NIG for the Italian population; ii) definition of pathogenicity by ACGM or the Clinvar and the Varsome databases; iii) functional studies of the literature; iv) loss of heterozygosity (LOH) of a region encompassing the gene in the tumor tissue.

Results: We identified by NGS eight pathogenic variants (PVs) in the following genes: BRCA1, BRIP1, CDKN2A, CHEK2, FLCN, SBDS, SLX4 and VHL. PVs carriers represent approximately 7% of the patients (8/113). The patient with a family history of mesothelioma carried a canonical splice-site variant (c.38-1 G>T) in BAP1 that has never been reported. Five of these genes (BRCA1, BRIP1, CHEK2, SLX4, BAP1) are involved in the homologous recombination repair (HRR) pathway (55.5%), that repairs double strand breaks in DNA caused by asbestos. Studying the entire panel of our patients, i.e. including also those reported in Betti et al. 2017 and 2018, PVs carriers (23/212) show a statistically significant lower asbestos exposure in comparison to non-mutated patients (p<0.0001).

Conclusions: Overall, these data suggest that patients with germline mutations in DNA repair genes are less proficient to repair the DNA damage induced by asbestos and show increased susceptibility to asbestos-induced MPM. The identification of a subset of patients who carry predisposing mutations in the DNA repair genes may distinguish patients who can benefit from drugs that induce synthetic lethality.

malignant pleural mesothelioma, DNA repair genes, NGS, inherited cancer syndrome
**MS07.10: Malignant Pleural Mesothelioma With Genomic Near-Haploidization: A Newly Recognized Subset With Distinct Histologic, Clinical, and Genomic Features**


1Memorial Sloan Kettering Cancer Center, New York, United States

**Parallel Mini-Symposia 07: Recent Developments: Genetics and Biomarkers, Virtual, May 8, 2021, 12:30 AM - 2:00 AM**

**Objectives:** We assessed the histologic, clinical, and molecular features of malignant pleural mesothelioma (MPM) with genomic near-haploidization (GNH), an entity first defined in 2018 by the TCGA project.

**Methods:** We analyzed prospective clinical genomic profiling data from 237 MPM patients studied from 2014 to 2020 using the FDA-cleared MSK-IMPACT targeted NGS assay. Allele-specific copy-number analysis was performed using the FACETS algorithm, and GNH was defined as >80% genome-wide loss of heterozygosity. All GNH tumors were also analyzed using the Infinium MethylationEPIC (850K) DNA methylation array platform and compared to MPMs from the TCGA cohort. Tumors with evaluable tissue were assessed for tumor infiltrating lymphocytes (TILs) (1+, 2+, 3+) and necrosis.

**Results:** Out of 237 patients, 214 (90%) were evaluable for genome-wide allele-specific copy number analysis by FACETS. The distribution of histologies was as follows: epithelioid (n=158, 74%), biphasic (n=50, 23%), sarcomatoid histology (n=6, 3%). Notably, GNH was identified in 11 tumors (5%), all of which were biphasic. Compared to non-GNH biphasic tumors, GNH was associated with younger age (median of 58 years vs. 70 years, p=0.005) and less frequent history of self-reported asbestos exposure (18% vs. 74%, p=0.001). There was no difference in sex (females: 27% vs. 26%). Histologically, GNH MPM had a higher rate of 3+ TILs (90% vs. 22%, p=0.0001) and necrosis (91% vs. 41%, p=0.005). Genomic analysis revealed a higher frequency of pathogenic alterations in NF2 (91% vs. 46%, p=0.01) and TP53 (55% vs. 18%, p=0.02) in GNH MPM. As in the TCGA study, GNH tumors in the MSK cohort harbored alterations in SETDB1 (6/11, 55%), and these were present exclusively in this MPM subset. Array-based DNA methylation data showed that the MSK-GNH cases formed a distinct cluster with the three GNH cases from the TCGA study. Patients with GNH MPMs showed poor overall survival (11.7 months) that was similar to non-GNH biphasic MPMs (16.2 months, p=0.5) despite the younger age at diagnosis.

**Conclusion:** GNH defines a distinct, newly recognized subset of MPM typically arising in younger individuals with a lesser or absent history of asbestos exposure, and typically showing biphasic histology, high TILs, and necrosis. Consistent with prior reports, MPM with GNH are characterized by recurrent alterations in SETDB1, TP53, and NF2. Analysis of genome-wide DNA methylation data suggests that this subset of MPM is also epigenetically distinct.

**PL02.03: Switch Maintenance Gemcitabine after First Line Chemotherapy in Patients with Malignant Mesothelioma; Updated Results of a Multicenter Open Label Phase II Trial (NVALT19)**


1Netherlands Cancer Institute, Amsterdam, The Netherlands

2Isala, Zwolle, The Netherlands

3Erasmus University Medical Center, Rotterdam, The Netherlands

4Amphia hospital, Breda, The Netherlands

5Jeroen Bosch Hospital, ’s-Hertogenbosch, The Netherlands

6Deventer Ziekenhuis, Deventer, The Netherlands

7Maxima Medical Centre, Eindhoven, The Netherlands

8University of Groningen and University Medical Center Groningen, Groningen, The Netherlands

9ZGT Hengelo, Hengelo, The Netherlands

10Zuyderland Hospital, Geleen, The Netherlands

11Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands

12Catherina Hospital, , The Netherlands
Objectives: Platinum-pemetrexed doublet therapy is the standard first line therapy for patients with malignant pleural mesothelioma (MPM). However, over time all patients develop progressive disease after first line therapy. In the NVALT19 study, we examined whether switch maintenance gemcitabine in patients, who did not show progression after first line platinum-pemetrexed, could prolong time to disease progression.

Methods: The NVALT19 was a multicenter, open label, randomized phase II trial, conducted in 18 study centers in The Netherlands. Patients were randomized 1:1 between gemcitabine (1250 mg/m2 day 1 and 8 of 3 weekly schedule) or best supportive care (BSC), and stratified for histology, tumor response to first line therapy (complete + partial response versus stable disease) and treatment center. Gemcitabine was given until disease progression, severe toxicity or patient request for discontinuation. Main eligibility criteria were pathologically proven MPM, ECOG-PS 0-2 and completion of 4-6 cycles of first-line platinum-pemetrexed without progression. The primary endpoint was progression free survival (PFS) as determined by local physician according to modified RECIST for mesothelioma (mRECIST), clinical progression or death in the intention-to-treat population. It was computed that 118 events would yield 90% power to detect an increase in PFS from median 3.5 months to median 6 months at 90% confidence level.

Results: Between 20 March 2014 and 27 February 2019, 130 patients were randomized, 65 in each arm. PFS was significantly longer with gemcitabine (median 6.2 months) than with BSC (3.2 months; hazard ratio [HR] 0.48; 95% confidence interval [CI], 0.33 to 0.71; p =0.0002). The benefit was confirmed by independent central review (HR 0.49; 95% CI, 0.33 to 0.72; p=0.0002). Grades 3–4 adverse events occurred in 33 (51%) patients in the gemcitabine arm and in 10 (16%) patients in the BSC arm. An objective response was achieved in eight out of 48 patients (17%) with measurable disease receiving gemcitabine, and in two out of 50 patients (4%) in the BSC arm (p = 0.048). According to central review, an objective response was achieved in five out of 46 (11%) patients with measurable disease in the gemcitabine arm and in one out of 46 patients (2%) in the BSC arm. One patient died, likely due to a gemcitabine-related infection. Updated overall survival data will be presented at the iMiG conference 2021.

Conclusion: Switch-maintenance gemcitabine, after first-line chemotherapy, significantly prolonged progression-free survival compared to BSC alone, among patients with malignant mesothelioma. The study confirmed the activity of gemcitabine in treating malignant mesothelioma.

Keywords: Gemcitabine, Maintenance Therapy, Best Supportive Care, Malignant Mesothelioma

PL02.04: Impact and Inequalities: Findings from the Military Experiences of Mesothelioma Study

Taylor B1, Ejegi-Memeh S1, Tod A1, Darlison L1, Sherborne V1

1University Of Sheffield, Sheffield, United Kingdom

Objectives: Mesothelioma is a devastating condition both physically and psychologically. The UK reports the highest incidence rates of mesothelioma internationally. Symptom burden can be complex and severe and can have a profound impact on quality of life. Understanding the nature of the underlying cause, asbestos exposure, is challenging when the latency period is so long (20-50 years). Little is known about mesothelioma amongst UK military veterans. The Military Mesothelioma Experience Study (MiMES) is a qualitative interview-based study that aims to identify the care and support needs of UK military veterans. The Military Mesothelioma Experience Study (MiMES) is a qualitative interview-based study that aims to identify the care and support needs of UK military veterans from the perspective of veterans, family carers, health professionals and support agency staff.

Methods: This qualitative health services research study involved semi-structured interviews with 14 male military veterans with mesothelioma, who had been exposed to asbestos during their military career. Nine family carers and 8 health professionals were also interviewed.
Recruitment was conducted via trusted charitable organisations including Mesothelioma UK and Asbestos Support Groups. Interviews were transcribed, anonymised and analysed using Thematic Analysis techniques.

**Results:** MiMES participants reported how shocking and devastating the diagnosis of mesothelioma can be. However, many employed attributes and techniques to cope with the diagnosis that appeared rooted in their military background. These included taking an ‘action-based’ and planned approach to managing the diagnosis and symptoms. Goal focused responses helped participants maintain control over the illness and symptoms, enabled them to ‘not give up’ and helped them fight the condition. Maintaining control regarding treatment and trial options was important to the veterans. Direct, clear and honest information helped them to do this.

Some MiMES participants reported perceived inequalities when they compared themselves to civilians with mesothelioma. UK veterans diagnosed with Mesothelioma as a result of Service can choose between receiving a traditional War Pension, or £140,000 in lump sum compensation. All the MiMES patient participants had pursued a claim and been awarded a lump sum. They reported being unable to incorporate the cost of new treatments such as immunotherapy into their claim, as is possible for civilians. Some participants had served in the United States during their time in the UK Armed Forces. They considered the pension scheme and financial compensation for US veterans with mesothelioma to be better compared to the UK in terms of ease of process and amount awarded. Some participants thought veterans were generally treated better and more respected in the US than in the UK.

**Conclusion:** The findings provide valuable insight into the impact and coping mechanisms of UK veterans with a diagnosis of mesothelioma. Perceived inequalities create an additional challenge to managing and living with this complex condition.

**Keywords:** Mesothelioma, Quality of Life, disease impact

---

**PL03.05: The Role of Serum Mesothelin in Monitoring Patients Following Extended Pleurectomy Decortication for Malignant Pleural Mesothelioma: An Interim Analysis**


1University Hospitals of Leicester, Leicester, United Kingdom, 2University of Leicester, Leicester, United Kingdom, 3Fujirebio, Ghent, Belgium

**Plenary III: Surgery – Individualising Care Appropriately, Virtual, May 8, 2021, 1:00 PM - 2:30 PM**

**Objectives:** Malignant pleural mesothelioma (MPM) is an incurable cancer. Extended pleurectomy decortication (EPD) aims to remove all macroscopic disease, however, following resection, monitoring for disease progression is critical to the timing of adjuvant treatments. Currently, computerised tomographic scans (CT) are used, however radiological confirmation of disease progression can be difficult. Serum mesothelin monitoring has shown promise in this area. The aim of this study is to prospectively analyse serial mesothelin measurements in patients undergoing EPD to determine if it can be used as a marker for disease progression.

**Methods:** A prospectively collated database of all chemonaive patients undergoing EPD for MPM since July 2017 was used. In this interim analysis, all patients recruited between July 2017 and March 2019 were analysed. Blood samples for serum mesothelin were obtained at 6 timepoints: pre-and post-operatively, 3, 6, 9 and 12 months. Alongside the three-monthly serum mesothelin samples, CT scans were scheduled to determine the radiological status. Serum mesothelin measurements were analysed using the Lumipulse® G600 (chemiluminescent enzyme immunoassay (CLEIA)) and performed at Fujirebio, Ghent, Belgium. Disease-free interval was calculated from the date of the operation until CT-evidence of disease progression or censor date. Overall survival was calculated from the date of the operation until the date of death or censor date. Descriptive statistics were used to analyse the demographic and pre-operative data. Categorical data was analysed using Pearson Chi-Square, otherwise
the Fisher's exact test was used. Continuous data was analysed using the Mann-Whitney U test. Univariate analyses were performed using the Kaplan-Meier method with the log rank test. All statistical analyses were performed using SPSS Version 25.

**Results:** Over a period of 20 months, 23 chemonaïve patients with MPM treated by EPD were recruited (18 were male with a median age of 71 years (IQR: 65-75)). The most common histology was epithelioid disease in 22 patients. The median pre-operative and post-operative mesothelin level was 2.05 nmol/L (IQR: 1.1-7.28 nmol/L) and 0.77 nmol/L (IQR: 0.45-2.03 nmol/L), respectively. During a median follow-up of 284 days, seventeen patients had evidence of disease progression and eleven patients had died. The median disease-free interval was 272 days (SE: 44; 95%CI: 186-358 days) and the median overall survival was 589 days (SE: 129; 95%CI: 336-842 days). There were no differences in disease-free interval and overall survival when pre-operative mesothelin levels were dichotomised to <2 or >2 nmol/L (p=0.398 and p=0.58, respectively). The mesothelin level increase in those who had disease progression was non-significantly higher than those patients who did not (0.37 vs. 0.01, respectively, p=0.197).

**Conclusion:** In this interim analysis, we have shown that the serum mesothelin falls dramatically following EPD. There are no associations between pre-operative or postoperative mesothelin level and disease-free interval or overall survival. Although not significant, the mesothelin levels are 37% higher in those patients with evidence of disease progression than those patients who do not suggesting that mesothelin could be a useful biomarker for monitoring patients following surgery for MPM. With continued recruitment, this study will be able to determine the answer to this question.

**Keywords:** Malignant Pleural Mesothelioma, Surgery, Extended pleurectomy decortication, Mesothelin, Radiology

**PL03.06: Project 1 Surgical Mesothelioma Consortium: Long Term Survivor**

Opitz I1, Lauk O1, Werner R1, Battilana B1, Neuer T1, Batirel H2, Pass H3, Flores R4, Wolf A5, De Perrot M5, Hoda M6, Klepetko W5, Kiklovits T6, Hashimoto M7, Hasegawa S7, Rusch V8, Bueno R8

1University Hospital Zurich, Department Of Thoracic Surgery, Zurich, Switzerland, 2Marmara University Hospital, Department Of Thoracic Surgery, Istanbul, Turkey, 3Langone’s Perlmutter Cancer Center, New York City, USA, 4The Mount Sinai Hospital, New York City, USA, 5University of Toronto, Toronto, Canada, 6Medical University of Vienna, Division of Thoracic Surgery, Vienna, Austria, 7Hyogo College of Medicine, Hyogo, Japan, 8Brigham and Women’s Hospital, Division Of Thoracic Surgery, Boston, USA, 9Memorial Sloan Kettering Cancer Center, New York City, USA

**Plenary III: Surgery – Individualising Care Appropriately, Virtual, May 8, 2021, 1:00 PM - 2:30 PM**

**Objectives:** Multimodality therapy approach has been shown to have the best prognosis on overall survival (OS) in patients with malignant pleural mesothelioma of approximately 25 months. In this present analysis, we provide information about long-term survivors with 5 years survival rate of high volume centres around the world.

**Methods:** In this multicenter retrospective descriptive analysis of 8 different centers, long-term survivors were defined by an OS of ≥5 years from surgery on (60 months). Patients were intended to be treated within a multimodality therapy approach with curative intent. This included induction chemotherapy with/without radiotherapy, followed by macroscopic complete resection, either (extended) pleurectomy/decortication ((e)PD) or pneumonectomy (EPP) with or without the addition of intraoperative chemotherapy or photodynamic therapy, followed by radio- or immunotherapy in some of the centers. OS and progression free survival (PFS) was calculated with Kaplan Meier analysis.

**Results:** Out of high volume centers, 262 patients were identified as long-term survivors. The majority was of male gender (n=166, 63%) and had a median age of 59 (range 21-83) years at time of diagnosis. 232 patients were of epithelioid histotype versus 30 of non-epithelioid subtype
and in 58% it was located on the right side. At the end of this analysis, 148 patients were dead, 104 patients still alive and 10 patients were lost to follow-up. Induction chemotherapy was performed in 71 patients followed by either (e)PD or EPP in 232 patients. Radiotherapy either in a neoadjuvant or as an adjuvant setting was performed in 14 and 90 patients, respectively.

The distribution of pathological tumor stages was as followed: pT1 (n=50), pT2 (n=63), pT3 (n=90) or pT4 (n=16). Affected lymph nodes were not seen in 150 patients with pN0, but 20 patients had pN1 and 39 patients had pN2. Three patient showed distant metastasis. The analysis showed a median OS from surgery until death or loss to follow up of 100 months (95% CI: 93-108 months) given 5-year survival. The median PFS was 58 months (95% CI: 47-71 months, missing values: 164) from surgery in patients with 5 year survival.

Conclusion: Despite this highly aggressive, non-curable, disease associated with poor prognosis, long-term survivors with a median OS of 100 months represent cohort, which most likely benefit from a multimodality therapy approach. Besides known clinical and molecular prognosticators, further investigations need to be pursued to identify these patients pre-therapeutically for a precise and individual therapy approach.

Keywords: Macroscopic complete resection, surgical treatment, longterm survivors, multimodality treatment

MS08.04: Tumour-Specific Effector Memory Cytotoxic T Lymphocytes (CTL) Associates with Successful Outcomes to Immune Checkpoint Blockade in a Murine Mesothelioma Model


1University of Western Australia, National Centre for Asbestos Related Diseases, Perth, Australia, 2Telethon Kids Institute, Perth, Australia, 3Murdoch University, Institute for Immunology & Infectious Diseases, Perth, Australia

Objective: Immune checkpoint blockade (ICPB) has shown success in multiple solid cancers. However, only a minority of patients display durable responses, and some cancer types seem to be less sensitive to ICPB than others. The efficacy of ICPB in mesothelioma is under investigation, with approximately 20% response rates to single agents in clinical trials. ICPB unleashes cytotoxic T lymphocytes (CTLs) from exhaustion to promote T cell mediated tumour cell killing. T cell activation is predicated on its T cell receptor (TCR) recognizing its specific antigen target. The immune system creates a repertoire of T cells, each with a variant TCR, that is specific for a particular antigen. As the T cell repertoire is highly variable between individuals, changes in TCR diversity and T cell phenotypes might contribute to the variability of response seen with ICPB. We studied pre-, post-treatment tumour-specific CTL proportions and phenotypes in relation to ICPB outcomes in a murine mesothelioma model.

Methods: To understand mechanisms that underlie successful responses to ICPB, our group developed a dual tumour model whereby inbred mice harbouring monoclonal tumours showed dichotomous responses to anti-CTLA4 and anti-PD-L1 ICPB. Tumours are inoculated bilaterally and respond to ICPB symmetrically. This allows the complete removal of a tumour from one flank pre- or post-treatment, with ICPB response in the resected tumour inferred from the remaining contralateral tumour. In this project, we used an AB1 mesothelioma cell line which has been stably transfected with a neo-tumour antigen (HA, hemagglutinin). Prior to tumour inoculation, we pre-seeded mice with a fixed precursor frequency of HA-specific CD8+ T cells. We studied pre-, post-treatment HA-specific CD8+ T cell phenotype and overall TCR repertoire diversity using flow cytometry and TCRβ sequencing respectively.

Results: ICPB increased the frequency of tumour infiltrating HA-specific, cytotoxic (granzyme B+) T cells. HA-specific T cells surprisingly occupied >40% of the tumour T cell repertoire in majority of mice post-treatment. However, frequencies of HA-specific T cells were not significantly different in responding compared to non-responding tumours or draining lymph nodes (DLNs), either pre- or post-ICPB. We further show that tumours and DLNs of responding mice were significantly enriched for HA-specific CTLs that displayed effector
memory (CD44hiCD62LloCD127+KLRG1+) and central memory (CD44hiCD62LloCD127+KLRG1-) phenotypes. Regulatory T cells were significantly reduced in responding tumours post treatment. There were no significant differences in cytotoxic (Granzyme B+), proliferating (Ki67+) or exhausted (PD-1+) HA-specific T cells between responding and non-responding tumours. We are currently analysing the overall T cell repertoire of responding and non-responding tumours. Results will be presented at the meeting.

Conclusion: Although ICPB can increase tumour-specific CTLs, our study suggests that skewing the T cell repertoire against a single specificity does not necessarily result in durable responses to ICPB. Driving differentiation of tumour-specific T cells towards a memory phenotype, in the presence of reduced immunosuppression might be key to successful ICPB outcomes in mesothelioma.

Methods: Two-hundred eleven MPM whole tissue RNA-sequencing (wtRNA-seq) transcriptomes across the histologic spectrum were analyzed. Of these, 181 had clinicopathologic data available; three of 181 were excluded from initial analysis due to subsequent treatment with immunotherapy. Slides from the remaining 178 tumors were stained for PD-L1 (clone 405.9A11, Cell Signaling, MA, USA; 1:200 dilution), and expression in ≥1% of tumor cells as determined by a pulmonary pathologist (masked to clinical annotation) was considered positive. To stratify tumors for differential expression analysis (DGE), samples were divided into quartiles by CD274 wtRNA-seq expression level. DGE between the first and fourth quartiles was performed controlling for prognostic clinical and molecular features including the published C/V score (Bueno et al, 2016), which significantly differentiates MPM tumors by cluster of expression related to epithelial/mesenchymal phenotype. Genes with an FDR<0.1 were considered significant. Consensus clustering was performed to determine the optimal number of sample subclusters. Hierarchical clustering was performed with Euclidean distance and Ward.D2 linkage, and visualized using the “pheatmap” R package.

Results: PD-L1 staining was positive by IHC in 23/178 (12.9%) of tumors. Following DGE analysis between samples in the first and fourth quartiles of CD274 expression, 171 genes met the threshold for significance. The top 10 significantly differentially expressed genes were CD274, WARS, TAP1, BATF4, PARP12, CXCL10, OASL, CCL8, GBP1, and GBP5. Immune checkpoint genes TIGIT, LAG3, CTLA4, and ICOS were also significantly upregulated in samples demonstrating high CD274 expression. Unsupervised hierarchical clustering using these 171 genes revealed clear discrimination between samples with high and low CD274 expression. Furthermore, samples with high CD274 expression and low CD274 expression each split into several distinct

MS08.05: High PD-L1 (CD274) RNA Expression is Associated with Diverse Transcriptional Phenotypes in Malignant Pleural Mesothelioma

Wadowski B1, Severson D1, Hung Y2, Chirieac L1, Levy R1, Gustafson C1, Richards W1, De Rienzo A1, Bueno R1

1The Thoracic Surgery Oncology laboratory and the International Mesothelioma Program (www.impmeso.org), Division of Thoracic Surgery and the Lung Center, Brigham and Women’s Hospital and Harvard Medical School, Boston, United States, 2Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, United States

Parallel Mini-Symposia 08: Immunotherapy and Checkpoint Blockade, Virtual, May 8, 2021, 2:30 PM - 4:00 PM
clusters. Fifty-eight (37.4%) of IHC-negative tumors fell into CD274-high transcriptomic clusters, along with 20/23 (87%) of IHC-positive tumors. IHC-positive tumors were distributed unevenly among different CD274-high transcriptomic clusters.

**Conclusion:** PD-L1 RNA expression is associated with significant differential gene expression including several known mediators of anti-tumor immunity. We show that MPM expressing high levels of CD274 exhibit heterogeneity at the transcriptome level. This heterogeneity cannot be discerned using IHC alone. Further analyses aim to investigate whether response to immunotherapy is related to the immune phenotypes associated with different clusters of PD-L1 positive samples.

**PD-L1; immunotherapy; transcriptomics; biomarkers; checkpoint; immune; molecular**

**MS08.06: Targeting Small Pleural Macrophages in an Intrathoracic Murine Malignant Pleural Mesothelioma Model**

Kohno M1,2, Murakami J2, Wu L2, Chan M2, Yun Z2, de Perrot M1,2

1Division of Thoracic Surgery, Toronto General Hospital, University Health Network, Toronto, Canada, 2Latner Thoracic Surgery Research Laboratories, Toronto General Research Institute, University of Toronto, Toronto, Canada

**Objectives:** Tumor-associated macrophages (TAMs) possess tumour-promoting functions including stimulation of tumour cell proliferation, angiogenesis, tumor cell invasion and immunosuppression. We have developed an intrathoracic murine mesothelioma model to investigate the tumor immunity locally in the pleural space. This model has the advantage to provide the pleural effusion as a good surrogate of the tumor microenvironment. The role of TAMs in mesothelioma development and the mesothelioma microenvironment in the pleural cavity has not yet been fully addressed. Our aims in this study were to elucidate the kinetics of TAMs in the pleural effusion after tumor cell injection, and to develop a new therapeutic approach targeting tumor-infiltrating myeloid cells in our intrathoracic mesothelioma model.

**Methods:** Balb/c mice were injected with 0.5 × 10^6 of AB12 murine malignant mesothelioma cell line into the pleural cavity. Pleural effusion was collected at different time points after tumor cell injection, and the proportion of TAMs were determined by flow cytometry. We performed single-cell RNA-sequencing on pleural lavage fluid 3 days after tumor cell injection to define the cellular determinants of TAMs in an unbiased manner. CCR2 antagonist (RS 504393), anti-mouse CCL2 (MCP-1) antibody or anti-mouse CSF1R (CD115) antibody was injected i.p. to the intrathoracic mesothelioma model mice and survival analysis was carried out in lieu of tumor burden assessment to compare treatment groups. Tissue samples were collected, and flow cytometry was performed for analyses.

**Results:** F4/80+CD68+ macrophages increased gradually up to day 10 before falling on day 14. On the other hand, the level of F4/80+CD68+CD206+ M2 macrophages was stably low up to day 7 and increased dramatically on day 10 and 14. Within F4/80+ population, we found two subsets that differ in F4/80 expression level. Under homeostatic conditions, F4/80high cells were the major pleural macrophage population; however, F4/80low cells rapidly increased on day 3 after tumor cell injection. Based on size difference determined by forward scatter profile, F4/80low cells are smaller than F4/80high cells. We can refer to F4/80low cells as small pleural macrophages and F4/80high cells as large pleural macrophages.

Furthermore, F4/80low cells displayed high surface levels of MHC class II and the proportion of CD206+ in F4/80low cells dramatically increased on day 10 and 14. Clustering analysis of single-cell RNA-sequencing distinguished small and large pleural macrophage populations. CCR2 was highly up-regulated in small pleural macrophage population compared with large pleural macrophages. Administration of CCR2 antagonist reduced blood inflammatory monocytes and slightly attenuated recruitment of small pleural macrophages in early phase, but did not show prolonged survival. The survival was not significantly different among the mice treated with anti-CCL2 antibody or anti-CSF1R antibody and those injected with control IgG.
CONCLUSION: TAMs dramatically accumulate in the tumor microenvironment during mesothelioma progression. F4/80low macrophages contribute to a large proportion of M2 macrophages. At the single-cell level, small pleural macrophages specifically expressed high level of CCR2. Monotherapy of CCR2 antagonist, anti-CCL2 antibody or anti-CSF1R antibody failed to demonstrate prolonged survival. We are investigating the effects of these agents in combination with conventional chemotherapy and immunotherapy.

KEYWORDS: tumor-associated macrophages, myeloid-derived suppressor cells, pleural effusion, single-cell RNA sequencing

MS09.04: Interim Results of Phase II Trial for Novel Magnetic Resonance Imaging of Peritoneal Mesothelioma

Dhiman A, Berger Y1, Harmath C1, Sherman S1, Medved M1, Hindi E1, Engelmann R1, Eng O1, Fenton E1, Karczmar G1, Kindler H1, Armato S1, Oto A1, Straus C1, Turaga K1
1University of Chicago, Chicago, United States

Parallel Mini-Symposia 09: Peritoneal Mesothelioma, Virtual, May 8, 2021, 2:30 PM - 4:00 PM

OBJECTIVES: Current cross-sectional imaging demonstrates poor sensitivity for peritoneal disease which often requires laparotomy/laparoscopy to accurately detect and quantify peritoneal tumor burden. We report interim results of a novel method utilizing high resolution (HR) MRI to detect peritoneal mesothelioma.

METHODS: Patients with malignant peritoneal mesothelioma (MPM) undergoing laparoscopy/laparotomy were enrolled in a single arm Phase II prospective clinical trial (NCT03867578). During the exploratory phase, MRI scans obtained from the first 5 patients were used to optimize coil positions, sequence parameters and contrast timing. Novel elements of our finalized MRI protocol included: double dose injection of Dotarem; pre-contrast free breathing HR coronal T2 weighted sequences without fat suppression; and 3D T1 HR coronal sequences, acquired in 3 breath holds at multiple post-contrast time points (range 2-18 minutes) using mDixon technique and focused on the right diaphragm / liver dome. Sensitivity was assessed by a blinded radiologist on the remaining cohort. Post scanning image processing is currently being performed.

RESULTS: Ten patients (out of planned 21) with epithelioid type MPM (7 males, median age 57 (range 43-67) years, median BMI 30.4 (range 23.9-38.9) kg/m2) were enrolled between 2/2019-9/2019. MRI was performed 3 (range 1-17) days before laparoscopic (n=6) or open (n=4) surgery. The median intraoperative peritoneal cancer index score was 34 (range 9-39). One patient was excluded from the analysis due to failed laparoscopy. Review by a blinded radiologist yielded a per-region sensitivity of 8/9 (89%) for the right diaphragm region and 6/6 (100%) for the pelvis. During the study period, no procedure-related or contrast-related adverse events were reported.

CONCLUSION: Our HR MRI protocol is tolerable, safe and may increase the diagnostic sensitivity of MPM detection. Final results from this ongoing study will allow to compare sensitivities with standard of care imaging.

KEYWORDS: Mesothelioma, Peritoneal, Imaging, MRI, Magnetic Resonance Imaging, Sensitivity

MS09.05: Bap1+/- GEM Mice Exposed to Minimal Doses of Crocidolite or Chrysotile Asbestos Exhibit Increased Susceptibility to Peritoneal Mesothelioma Induction

Kadariya Y1, Cheung M1, Testa J1, Seiphoori A2, Jerolmack D2
1Fox Chase Cancer Center, Philadelphia, PA 19111, USA; 2University of Pennsylvania, Philadelphia, USA

Parallel Mini-Symposia 09: Peritoneal Mesothelioma, Virtual, May 8, 2021, 2:30 PM - 4:00 PM

Bap1+/- GEM Mice Exposed to Minimal Doses of Crocidolite or Chrysotile Asbestos Exhibit Increased Susceptibility to Peritoneal Mesothelioma Induction

Yuwaraj Kadariya1, Mitchell Chueng1, Ali Seiphoori2, Douglas Jerolmack2, Joseph R. Testa1
1Fox Chase Cancer Center, Philadelphia, PA 19111, USA; 2University of Pennsylvania, Philadelphia, USA
Malignant mesothelioma (MM) has long been known to be associated with exposure to various forms of asbestos fibers. The discovery of Bap1 as a predisposition gene for the development of familial mesothelioma prompted us to explore the idea of gene-environment interactions in a Bap1 GEM mice model, using two different forms of carcinogenic asbestos: crocidolite and chrysotile.

**Objectives:** The goal of this investigation was to test whether minimal exposures to crocidolite and/or chrysotile can significantly increase the incidence and rate of onset of malignant peritoneal mesothelioma in a germline Bap1 heterozygous mouse model.

**Methods:** Bap1 heterozygous (Bap1+/-) mice were crossed to Bap1 wild type (Bap1+/+) mice of the same genetic background. Bap1+/+ and Bap1+/- littermates were chronically injected (8 times with 3-week intervals between injections) intraperitoneally with asbestos at total doses of 0.1 and 0.8 mg crocidolite and 0.4 mg chrysotile. Mice were then monitored for the development of tumor over time. Diagnosis of MM was confirmed by H&E and immunohistochemistry with various markers such as WT1, mesothelin, and cytokeratins.

**Results:** For mice exposed to crocidolite at 0.8 mg, peritoneal MMs were observed in 19 out of 21 (90%) Bap1+/- mice compared to 12 of 22 (55%) of Bap1+/+ littermates (p<0.01). At the lower dose (0.1 mg), MM incidence in Bap1+/- was 44% (8/18 mice), as compared to 13% (2/16) in Bap1+/+ mice (p<0.001). With low-dose chrysotile (0.4 mg), peritoneal MMs were identified in 16 of 18 (89%) of Bap1+/- mice versus only 5 of 15 (33%) Bap1 wild type animals (p<0.004). With each form of asbestos and at all doses, tumor onset occurred at a statistically significant earlier time frames in the Bap1-mutant mice.

**Conclusion:** Collectively, these findings suggest that germline Bap1 mutation increases asbestos-induced MM susceptibility and onset rate upon minimal exposure to either crocidolite or chrysotile fibers.
50% (19/38) for PD-L1 and 89% (34/38) for VISTA. 76% (29/38) had loss of BAP1 including 7 cases which were WT on NGS. OS in MPeM was stratified by several genes altered vs WT) including CDKN2A/B (n=4 vs 46, 20.1 vs 58.0 months respectively; p=0.45), TP53 (n=8 vs 42, 62.2 vs 50.4 months; p=0.45) and BAP1 (n=30 vs 20, 62.2 vs 58.0 months; p=0.35). When combining NGS and IHC findings, OS was significantly worse in patients with BAP1 alteration/loss compared to WT/retained (n=37 vs 13, 43.8 vs 117.3 months; p=0.03). 13% (4/30) of patients with germline data were found to have a pathogenic variant: 3 MPeM (POT1 I78T, MUTYH R109Y, BAP1 E402*) and 1 WDPM (APC I1037K).

Conclusion: NGS confirms the distinct biology of MPeM and WDPM. MPeM demonstrated few cell cycle (CDKN2A/B) alterations (8%). BAP1 alteration/loss was associated with shorter survival in MPeM. There was a notable minority of patients with MPeM with GNH with an association with NF2, TP53 and SETDB1 mutations. All TRAF7 alterations occurred in WDPM, however, not all WDPM harbored an alteration. Consistent with other reports, the prevalence of germline alterations was 13%. These data show some notable distinctions from reports on MPM and should be further investigated.

Peritoneal Mesothelioma, Next Generation Sequencing combined with hyperthermic intraperitoneal chemotherapy. Due to the rarity of the condition, little has been published on the clinical presentation and behaviour over time, nor the optimal treatment approach.

Methods: Retrospective analysis of a prospective peritoneal malignancy data base between 2001 and 2019. Details on all patients with cystic mesothelioma as a definitive diagnosis after CRS and HIPEC were analysed. Prior interventions were documented. Mode of presentation, surgical treatment and post-operative outcomes were analysed. Follow up consisted of annual abdominal CT and tumour markers.

Results: Overall 40 patients underwent CRS and HIPEC between 2001 to 2019 for multicystic mesothelioma. There were 25 females and 15 males of median (range) age 41.5 years(21-69). The mode of presentation included incidental findings on CT in 2, incidental findings during surgery in 6, investigation for abdominal pain, distension or bloating in 29. Six patients had prior interventions at their referral hospital. CRS involved peritonectomy in all 40. 7/40 had a temporary or permanent stoma. 36 patients underwent a CC0 resection while 4 had a CC1. Median follow-up period was 65 months. There were no deaths in the follow-up period. The Kaplan Mier predicted recurrence free interval is 111.0 months.

Conclusion: Multicystic mesothelioma is a rare peritoneal neoplasm with a heterogenous presentation pattern. CRS and HIPEC is a safe and effective management option for this group of patients with favourable long term survival.

Keywords: Multicystic mesothelioma, surgery, outcomes, CRS, HIPEC

MS09.07: Outcomes in 40 Patients with Multicystic Peritoneal Mesothelioma Treated by Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Zahid A1, Cecil T1, Carr N1, Moran B1

1Peritoneal Malignancy Institute, Basingstoke, United Kingdom

Parallel Mini-Symposia 09: Peritoneal Mesothelioma, Virtual, May 8, 2021, 2:30 PM - 4:00 PM

Objectives: Multicystic mesothelioma is a rare peritoneal neoplasm with ongoing debate as to the aetiology, need for intervention and nature of the pathology. Experience over time suggests that it a borderline malignancy, best treated by cytoreductive surgery to remove macroscopic disease
MS09.08: Surgical Phenotype of Patients with Malignant Peritoneal Mesothelioma and a Germline Mutation

Berger Y1, Gadiraju M1, Dhiman A1, Gilliam K1, Rose B1, Chen H1, Helgeson M1, Eng O1, Husain A1, Drazer M1, Kindler H1, Churpek J1, Turaga K1

1University of Chicago, Chicago, USA

Parallel Mini-Symposia 09: Peritoneal Mesothelioma, Virtual, May 8, 2021, 2:30 PM - 4:00 PM

Objectives: The surgical phenotype of malignant peritoneal mesothelioma (MPM) patients with germline mutations (GM) has not been studied previously. We aimed to investigate if MPM patients with GM have distinct characteristics when compared to those without GM.

Methods: MPM patients were selected from an ongoing prospective study that conducts germline testing of 85 susceptibility genes. Germline status was correlated with surgical data obtained from a prospectively collected database using univariate analyses. Significant clinical factors were explored to find the ideal multi-variable combination predicting the presence of BAP1 GM.

Results: Out of 88 MPM patients enrolled between 2009-2019, 18 GMs (20.5%) were identified. BAP1 was the gene most frequently mutated (n=11, 12.5% of all patients). The remaining mutations were in WT1, CDKN2A, CHEK2, ATM, BRCA2 (n=1 patient each) and SDHA (n=2 patients). Surgical procedures (n=83) were performed in 71 patients, the most common of which were cytoreductive surgeries with hyperthermic intraperitoneal chemotherapy (n=61). Baseline characteristics were similar between the GM and no GM (n=70) groups excluding higher prevalence of...
other prior cancers (61.1% vs. 31.4%, p=0.02) and lower baseline platelet count (251 (160-413) vs. 367 (196-780), p=0.005) in GM patients. Median overall survival did not differ significantly between GM and no GM patients (not reached vs. 46.7 months, respectively, p=0.61).

Disparities in baseline and intraoperative characteristics between patients with BAP1 GM and those without GM are presented in Table 1. On receiver operating characteristic (ROC) analysis, the combination of the peritoneal cancer index, platelet count and bicavitary disease yielded an area under the curve (AUC) of 0.98 (95%CI 0.95-1.0) for BAP1 GM detection among operated MPM patients (Figure 1).

**Conclusion:** GM play a pathogenic role in a substantial proportion of MPM patients. Higher tumor burden, bicavitary disease and lower platelet count are suggestive of BAP1 GM and should prompt germline testing.

Mesothelioma, Peritoneal, Malignant, Germline, Mutation, BAP1, Surgery
**Abstracts**

**MS10.04: Symptom Burden and Unmet Needs in MPM: Exploratory Analyses from the RESPECT-Meso Study**

**Hoon S**1,2, Lawrie I3, Qi C4, Rahman N5,6, Maskell N7, Forbes K8, Gerry S4, Chauhan A9,10,11, Brims F1,2

1Sir Charles Gairdner Hospital, Nedlands, Australia, 2Curtin Medical School, Curtin University, Perth, Australia, 3Department of Palliative Medicine, North Manchester General Hospital, Manchester, UK, 4Centre for Statistics in Medicine, University of Oxford, Oxford, UK, 5Oxford Respiratory Trials Unit, University of Oxford, Oxford, UK, 6National Institute for Health Research Oxford Biomedical Research Centre, Oxford, UK, 7Department of Respiratory Medicine, University of Bristol, Bristol, UK, 8Department of Palliative Medicine, University of Bristol, Bristol, UK, 9Department of Respiratory Medicine, Portsmouth Hospitals NHS Trust, Portsmouth, UK, 10Research & Innovation Department, Portsmouth Hospitals NHS Trust, Portsmouth, UK, 11School of Health Sciences and Social Work, University of Portsmouth, Portsmouth, UK

**Parallel Mini-Symposia 10: Symptoms and Pleural Management, Virtual, May 8, 2021, 2:30 PM - 4:00 PM**

**Objectives:** Malignant Pleural Mesothelioma (MPM) has a poor prognosis and high symptom burden. RESPECT-Meso was a large multicentre randomised study examining the role of regular early specialist palliative care on quality of life (QoL) with MPM. This is a planned exploratory analysis of the symptom burden and unmet needs identified from RESPECT-Meso participants.

**Methods:** Exploratory analysis from 173 participants used the General Health Status (GHS) measure (from the EORTC QLQ-C30 QoL questionnaire) and 86 participants using the Sheffield Profile for Assessment and Referral to Care (SPARC) and the revised Edmonton Symptom Assessment System (ESAS) questionnaires in those randomised to SPC. Eligibility for the RESPECT-Meso study included confirmed MPM with diagnosis ≤6 weeks prior, ECOG PS 0 or 1 and no significant physical or psychological comorbidity.

Univariable and multivariable Cox proportional hazards models were derived for the transformed GHS, physical symptom scores and composite measures of physical, psychological and social to examine for any relationship with survival. Spearman’s rho was used to examine correlation between the measures. Free text was assessed using content analysis, looking for common themes and words.

**Results:** Participants were predominantly male (79.9%), mean age 72.6 years, ECOG PS was 0 in 38%, 78% of MPM was epithelioid. At least three symptoms were reported in 69.8% of participants.

Physical symptoms included fatigue (81%), dyspnoea (73.3%), pain (61.2%), weight loss (59.3%). Anxiety was reported by 54.7% of participants, 52.3% reported low mood and 48.8% reported anhedonia symptoms.

Reported physical symptoms demonstrated high correlation (for instance weight loss with loss of reduced appetite, dyspnoea; all p<0.005). The univariable Hazard Ratio (HR) (for death) of reduced appetite was 2.3 (1.2-4.4; p=0.01); loss of weight 1.8 (0.98-3.4; p=0.06); dyspnoea 1.9 (1.1-3.5; p=0.03); pain 1.5 (0.8-2.9; p=0.19) and fatigue 2.5 (1.4-4.4; p=0.003). After multivariable adjustment for age, gender, PS, chemotherapy, sarcomatoid containing histology, comorbidities and baseline GHS, only pain remained statistically significant with a HR 2.9 (1.3-6.7; p=0.01). For each 1 unit increase in GHS score, the estimated HR for death was 0.987 (95% CI: 0.978, 0.996), p=0.006, indicating a worse reported QoL is related to shorter survival.

Unmet needs were common: 25.9% wanted more information about their condition, 24.7% about their care, 21.2% about their treatment and 16.3% about prognosis; 79.1% were concerned about the effect of their illness on family.

**Conclusion:** There is a high symptom burden in this study population at diagnosis, despite good baseline performance status. A worse QoL is associated with a worse survival. Unmet needs are common, perhaps highlighting a need for improved communication and information sharing.
MS10.05: Retrospective Study on Decision Tree Analysis Prognostic Scores in Malignant Pleural Mesothelioma - a DGH UK Perspective

Rajagopalan P¹, Ali R²

¹Barts And Royal London Hospital NHS Trust, London, United Kingdom, ²Imperial College Healthcare NHS Trust, London, United Kingdom

Parallel Mini-Symposia 10: Symptoms and Pleural Management, Virtual, May 8, 2021, 2:30 PM - 4:00 PM

Objectives: The decision tree analysis (DTA) model is a recent clinical tool developed by Brims et al (2016) making use of readily available clinical data to predict prognosis in newly diagnosed mesothelioma. We wanted to assess the clinical utility of DTA in predicting prognosis in our cohort of Malignant Pleural Mesothelioma (MPM) patients in three District General hospitals in UK.

Methods: Newly diagnosed cases of malignant pleural mesothelioma (MPM) presenting to one of three district general hospitals (DGH’s) within a trust in Southeast England were retrospectively identified over a 3-year period (January 2015 to December 2017). Patient records were reviewed and cases were grouped according to the decision tree analysis model.

Results: Fifty cases of MPM were identified, 43 cases (86%) were histologically confirmed, in the remaining seven cases a clinical diagnosis was made based upon radiology and cytology. All cases were discussed at multidisciplinary meetings within the trust. The majority of patients (76%) were male with a median age at presentation of 75.6 (range 46.4-95.1). Overall, the histological sub-types in this cohort were as follows: epithelioid (n=35), biphasic (n=5), sarcomatoid (n=3) and undefined (n=7). In all cases, patients had a pleural effusion on presentation, 26/50 right-sided, 18/50 left-sided and 3/50 bilaterally. The 50 cases were stratified according to the decision tree analysis model into the following groups: 2a (n=14), 2b (n=6), 3 (n=19), 4a (n=2), 4b (n=2), 4c (n=7). Survival rates at 18 months after diagnosis were as follows: 2a (42.9%), 2b (50%), 3 (26.3%), 4a (50%), 4b (0%), 4c (0%). Table 1 allows for comparison with the Brims derivation cohort.

Conclusion: In this cohort in three DGH’s with a moderate burden of mesothelioma, the decision tree analysis model was a good predictor of 18-month survival, discrepancies in survival rates may be explained by the small sample size of this cohort in comparison to the derivation cohort.

We would recommend that it is used more widely to help clinicians prognosticate in new diagnoses of MPM.

<table>
<thead>
<tr>
<th>Group</th>
<th>DGH Cohort N=</th>
<th>18-month survival rate (%)</th>
<th>Brims Derivation Cohort N=</th>
<th>18-month survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>14</td>
<td>42.9</td>
<td>30</td>
<td>86.7</td>
</tr>
<tr>
<td>2b</td>
<td>6</td>
<td>50.0</td>
<td>28</td>
<td>46.6</td>
</tr>
<tr>
<td>Group 2 overall</td>
<td>20</td>
<td>45.0</td>
<td>151</td>
<td>50.3</td>
</tr>
<tr>
<td>Group 3</td>
<td>19</td>
<td>26.3</td>
<td>171</td>
<td>28.1</td>
</tr>
<tr>
<td>Sub-group 4a</td>
<td>2</td>
<td>50.0</td>
<td>27</td>
<td>11.1</td>
</tr>
<tr>
<td>Sub-group 4b</td>
<td>2</td>
<td>0.0</td>
<td>29</td>
<td>6.9</td>
</tr>
<tr>
<td>Sub-group 4c</td>
<td>7</td>
<td>0.0</td>
<td>47</td>
<td>4.3</td>
</tr>
<tr>
<td>Sub-group 4d</td>
<td>0</td>
<td>0.0</td>
<td>27</td>
<td>0.0</td>
</tr>
<tr>
<td>Group 4 overall</td>
<td>11</td>
<td>9.1</td>
<td>130</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Table 1: Comparison of 18-month survival rates between Brims’ derivation cohort and the DGH cohort of interest in this study.
MS10.06: Improving Survival Is Not the Only Relevant Outcome for Patients Suffering from Malignant Pleural Mesothelioma and Their Caregivers: An Explorative Study (PointInMe_Explor)

Grosso F1, Rota G2, Crivellari S3, Lia M1, De Angelis A3, Kasa A, Cassinari A, Bertolotti M3, Muzio A4, Maconi A3, Budel P2

1Mesothelioma Unit, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, EU, 2Hospice Monsignor Zaccheo - ASL-AL, Casale Monferrato, Italy, EU, 3IRFI , Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, EU, 4Ospedale Santo Spirito, Casale Monferrato, Italy, EU

Parallel Mini-Symposia 10: Symptoms and Pleural Management, Virtual, May 8, 2021, 2:30 PM - 4:00 PM

Objectives: The study was aimed at exploring the patients' and caregivers' expectations on treatment outcomes, the understanding of the information delivered by the oncologists during the first and reevaluation visits and the role of the general practitioners (GP) in the management of patients suffering from advanced Malignant Pleural Mesothelioma (MPM) in the area of Casale Monferrato, in the North West of Italy, where the incidence of mesothelioma is more than 30 times higher than the median incidence in Europe. A multiprofessional mesothelioma unit involving specialists and also GPs has been created since 2012 to globally assist patients in each step of the diagnostic and therapeutic process. This study was conducted to better understand the need of MPM patients in our area and their satisfaction about the care provided within the unit.

Methods: Patients and caregivers were asked to fill in a multiple-choice questionnaire after the first visit or the re-evaluation visits (the ones in which a new treatment program was communicated) asking what is most important as the result of treatment, how much the oncologist was clear in communicating the diagnosis, the therapeutic options, the side effects, the role of the GP in supporting the care process and the trust-relationship with both the referral oncologist and the GP. Patients were also asked about the importance of having a referral caregiver.

Results: From March to August 2019, 31 consecutive patients, 18 males and 13 females, median age 71 (IQR 66-75) and 29 caregivers, 7 males and 22 females, median age 63 (IQR 49-67) were enrolled in the study. Improving survival was the most relevant expected outcome in 48% and 69% of patients and caregivers, respectively followed by maintenance of the quality of life (38% and 17%), having the minimal number of accesses in the hospital as possible (8% vs 4%) and improving symptoms (6% and 10%). Seventy-seven% of patients and 72% of caregivers stated that the communication of the diagnosis was very clear, 74% of patients and 72% of caregivers stated that explanations about treatments were very clear, 90% of both patients and caregivers stated that the communication of side effects was sufficiently clear. Ninety% of patients and 86% of caregivers are completely satisfied about the relationship with the referral oncologist whereas 58% of patients and 55% of caregivers are completely satisfied with the support given by the GP. Ninety-three% of patients think that having a referral caregiver is of utmost importance and 80% of patients appreciate the presence of a palliative expert in the patient-care team whereas 52% of patients think to require a psychological support.

Conclusion: This study highlights that in the high incidence area of MPM of Casale Monferrato, only half of advanced MPM patients and less that 2/3 of caregivers think that improving survival is the most relevant treatment outcome. The majority of patients and caregivers state to have clear information about diagnosis, treatment and related side effects and feel satisfied about the relationship with the specialists of the mesothelioma unit.

Keywords: Mesothelioma, caregiver, patient outcomes

MS10.07: An Integrative Systematic Review Exploring the Palliative Care Needs of Patients With Mesothelioma and Their Carers

Harrison M1, Gardiner C2, Taylor B1, Ejegi-Memeh S1, Darlison L2

1University Of Sheffield, Sheffield, United Kingdom, 2Mesothelioma UK, Leicester, United Kingdom
Parallel Mini-Symposia 10: Symptoms and Pleural Management, Virtual, May 8, 2021, 2:30 PM - 4:00 PM

Objectives: Palliative care needs are experienced by patients with mesothelioma and their families from the point of diagnosis through to the end of life. A randomised controlled trial found routine early referral to specialist palliative care did not improve quality of life or mood for mesothelioma patients when compared with standard care alone. One interpretation of this finding is that standard care is sufficient. In order to further understand what services are required by this unique patient group we sought to describe the palliative care needs of patients with mesothelioma and their families.

Methods: An integrative systematic review methodology was adopted. Four databases were searched, including: MEDLINE, CINAHL, PsycINFO and the Cochrane Library. Articles were included if they were published from 01 January 2000 to 10 May 2020 and presented empirical studies or comprehensive literature reviews including information about the palliative care needs of mesothelioma patients and their carers. All abstracts identified were screened for inclusion by one reviewer. Full texts were reviewed by two independent reviewers. The integrative method of extracting and synthesising data was followed; data reduction and extraction resulted in the development of a coding matrix, which was reviewed by two reviewers who explored patterns and themes in the data. Quality appraisal was conducted by two independent reviewers using established tools. The systematic review was registered on PROSPERO (CRD42020190115).

Results: The search identified 508 articles, 14 of which were included in the synthesis. ‘Uncertainty’ was identified as a cross-cutting theme resulting from the unpredictability around disease progression and when death would occur and compounded by patients and carers receiving insufficient information and not knowing who was responsible for co-ordinating their care. Five further themes were identified: management of care needs and high symptom burden; communication and information needs; organisation and co-ordination of services; consideration of the impact of seeking compensation; and the needs of family carers. Patients with mesothelioma and their carers identified that they wanted to receive a co-ordinated, team-based approach to palliative care with a named point of contact. Carers described the need to have the opportunity to communicate with specialist health professionals without the patient present, as well as the need for psychological and bereavement support. The included articles rarely distinguished between specialist palliative care and generalist palliative care, which is typically provided by thoracic and oncology teams. Furthermore, the terminology used in the articles suggests that palliative care provision was only recognised when delivered by specialist providers.

Conclusion: Limited evidence is available around the palliative care needs of patients with mesothelioma and their families with none of the included articles focussed specifically on answering this question. The findings of this review demonstrate the need to further consider the role non-specialist palliative care clinicians play in the provision of generalist palliative care to mesothelioma patients and their families. In addition, further exploration of the partnership working between specialist and generalist palliative care is warranted.

mesothelioma; palliative care; informal carers

MS11.05: MESOMICS Project: Deep Genomic Characterisation and Integration Unveil Specific Cancer Tasks and Evolutionary Traits, Together With Specific Morphological and Molecular Profiles With Important Clinical Implications

Mangiante L1,15, Alcala N1,15, Sexton-Oates A1,15, Di Genova A1,15, Giacobi C1, Le-Stang N2, Boyault S3, Tabone-Eglinger S2, Damola F2, Voegele C1, Alcala K1, NETMESO-MESOPATH INCa network, MESOBANK. Fr, Boland A4, Deleuze J4, Altmuller J5, Nuernberg P5, Ghostans A6, Cuenin C6, Maussion C7, Courtiol P7, Alexandrov L8, Lopez-Bigas N9, Lantuejoul S10, Hernandez-Vargas H11, Caux C12, Girard N13,14, Galateau-Salle F2, Foll M1,16, Fernandez-Cuesta L1,16

1Section of Genetics, International Agency for Research on Cancer - WHO, Lyon, France, 2Department of Pathology, Centre Léon Bérard (CLB), Lyon, France, 3Translational Research and Innovation Platform, Cancer Research Centre of Lyon (CRCL), Lyon, France, 4Centre National de Recherche en Génomique Humaine (CNRGH), Evry, France, 5Cologne Centre for Genomics (CCG), Cologne,
Parallel Mini-Symposia 11: Biomarkers and Genetics, Virtual, May 9, 2021, 12:30 AM - 2:00 AM

Objectives: The MESOMICS project for the multi-omic characterization of Malignant Pleural Mesothelioma (MPM) belongs to the Rare Cancers Genomics initiative (www.rarecancersgenomics.com) aiming at providing a better understanding of the molecular characteristics of rare cancers, such as MPM. Taking advantage of the expertise provided by a multidisciplinary team, and by means of state-of-the-art computational analyses as well as exceptional bio-repositories, our research is focused on: (1) identifying the molecular characteristics that may inform the carcinogenesis and aetiology of MPM; (2) providing the necessary data to generate a more clinically relevant classification of these tumours; and (3) improving the clinical management by identifying novel candidate diagnostic, prognostic, and predictive biomarkers.

Methods: We have generated whole-genome sequencing (WGS), RNA-seq, and 850k methylation arrays data for 120 MPM of the three main histological types (epithelioid, sarcomatoid, and biphasic) and main epithelioid morphological subtypes. Detailed morphological (including image-based AI scores), epidemiological (including probability, frequency, intensity, and duration of asbestos exposure) and clinical data is available for all the samples. Additionally, for 12 of the patients biological material is available for two tumoral regions allowing for intra-tumor molecular analyses.

Results: Through reanalyses of published data (Bueno et al. Nat Genet 2016; Hmeljak et al. Cancer Discov 2018), we have previously identified a continuum of molecular profiles that explained the prognosis of MPM better than any discrete model. The immune and vascular pathways were the major sources of molecular variation, with strong differences in the expression of immune checkpoints and pro-angiogenic genes (Alcala et al. EBioMedicine 2019). The analyses of WGS, RNA-seq, and methylation data for the 120 MPM novel samples from the MESOMICS series now provide the first integrative continuous characterisation of MPM unveiling an evolutionary trade-off (Hart et al. Nature Methods 2015) between very specific cancer tasks. This trade-off defines three phenotypic archetypes with specific molecular profiles with clinical implications. We also assess the contribution of evolutionary forces to MPM genomic profiles, highlighting how natural selection acts on hallmarks of cancer genes in some of the most aggressive cases, as well as showing variation in mutation rate influencing intra-tumor diversity within MPM, associated with specific molecular profiles. Additionally, we find evidence for genomic instability across all ‘omic layers in the most aggressive tumours. This MPM cartography identifies particular molecular characteristics related to the proportion of the acinar morphological variant. More globally, we find correlation with an AI prognosis score based on morphological features and this molecular map. Finally, WGS data, almost nonexistent for MPM, reveals the importance of genomic rearrangements in MPM as well as several chromothripsis cases, paving the way to a better understanding of the carcinogenesis of these tumours.

Conclusion: Considerable progress has been made in recent years in the molecular characterization of MPM. However, the lack of comprehensive studies investigating all the main molecular layers, such as the whole genome, have hampered the discovery of important findings for the clinical management of MPM. The MESOMICS project aims to fill these gaps to provide the missing pieces needed to tackle this aggressive disease.

MESOMICS project, Rare Cancers Genomics initiative, genomics, transcriptomic, methylome, evolution
MS11.06: Extracellular Vesicles as Novel Biomarkers in Malignant Pleural Mesothelioma

Ahmadzada T1, Sellwood M2, Reid G3, Clarke S1,4, Kao S1,5,6, Grau G1,2,7, Hosseini-Beheshti E1,2

1The University of Sydney, Camperdown, Australia, 2Vascular Immunology Unit, Department of Pathology, School of Medical Sciences, The University of Sydney, Camperdown, Australia, 3Department of Pathology, University of Otago, Dunedin, New Zealand, 4Department of Medical Oncology, Royal North Shore Hospital, Sydney, Australia, 5Department of Medical Oncology, Chris O’Brien Lifehouse, Sydney, Australia, 6Asbestos Diseases Research Institute, Sydney, Australia, 7The Sydney Nano Institute, The University of Sydney, Camperdown, Australia

Parallel Mini-Symposia 11: Biomarkers and Genetics, Virtual, May 9, 2021, 12:30 AM - 2:00 AM

Objectives: Extracellular vesicles (EV) are secreted by all cells (including cancerous cells) and carry various cargo from one cell to another. They include exosomes, microvesicles and oncosomes. EV have emerged as a novel mode of intercellular transport and communication. They can be found in all body fluids and are capable of being detected in liquid biopsies. EV are currently the subject of extensive research in several cancers for their potential role as tumour biomarkers, however there are limited studies so far on their role in malignant pleural mesothelioma (MPM). In particular, there are no studies to date concerning microvesicles and oncosomes in MPM. We aimed to characterize different classes of EV derived from five different MPM cell lines and patient plasma samples.

Methods: EV (exosomes, microvesicles and oncosomes) were isolated using classical centrifugation and ultracentrifugation from five MPM cell lines (NCI-H28, VMC23, MSTO-211H, NCI-H226, MM05) and the immortalized mesothelial cell line MeT-5A as a control. MPM patient plasma samples (n=9) were processed similarly to yield EV. Nanoparticle tracking analysis (NTA) was undertaken to determine numbers and size distribution of EV. Isolated EV were analysed using flow cytometry (FC) after staining with annexin V-FITC. Western blotting (WB) was performed to verify the presence of EV markers and MPM tumour biomarkers.

Results: NTA and FC results demonstrated major differences in the total number of exosomes, microvesicles and oncosomes released between different MPM cell lines as well as patient samples versus controls. We identified a group of MPM cell lines that are high EV producers (VMC23, MSTO-211H and NCI-H226) and a group of MPM cell lines that are low EV producers (NCI-H28 and MM05). Our results warrant further investigation into the mechanisms involved in the formation and release of different classes of EV and in the cargo sorting of EV derived from MPM cells. WB revealed, for the first time, the presence of important diagnostic and prognostic biomarkers in different classes of EV derived from MPM cells and plasma.

Conclusion: We show that MPM cells and plasma samples secrete different classes of EV that are potentially involved in intercellular communication and have great potential to serve as novel sources of non-invasive biomarkers in MPM.

Keywords: malignant pleural mesothelioma, extracellular vesicles, biomarkers, exosomes, microvesicles, oncosomes

MS11.07: Circular RNA as a Biomarker for Malignant Pleural Mesothelioma

Johnson B1, Yuen M1, Yu T1, McCaughan B2, Takahashi K1, Cheng Y1

1Asbestos Diseases Research Institute, Concord, Australia, 2School of Medicine, University of Sydney, Sydney, Australia

Parallel Mini-Symposia 11: Biomarkers and Genetics, Virtual, May 9, 2021, 12:30 AM - 2:00 AM

Objectives: Malignant pleural mesothelioma (MPM) is an aggressive cancer associated with poor prognosis and limited treatment options. MPM is difficult to diagnose and an invasive surgical or cytology procedure is required to obtain a definitive judgement. A novel class of non-coding RNA, circular RNAs (circRNAs), constitute a promising blood-based biomarker candidate for early detection of MPM. CircRNAs are highly stable in blood and there is growing evidence that indicates that their overexpression correlates with tumourigenesis for a range of cancer types. It has been proposed that circRNAs promote
tumourigenesis by binding to and impeding the function of tumour-suppressor microRNA (miRNA). Preliminary microarray data obtained by our lab have demonstrated a range of circRNAs that are upregulated in MPM cell lines. These upregulated circRNAs represent promising biomarker candidates that can potentially be utilised for the purpose of a non-invasive blood-based diagnosis of MPM. Therefore, the aim of this project is to develop a blood-based circRNA detection assay to detect the circRNA candidates (pre-selected from the microarray data).

**Methods:** A study of circRNA and microRNA correlation was carried out by bioinformatics analysis. The droplet digital PCR (ddPCR) technique was utilised to detect the pre-selected circRNA targets through the application of fluorescently-labelled probes that were designed to detect the unique backsplice junction sequence of the circRNA biomarker candidates. This detection assay was first performed on MPM primary cell lines, including immortalised mesothelial cells as a ‘normal’ reference control. Following the successful detection of the circRNA biomarker candidates within the cell lines, the assay was then applied to a range of MPM patient-derived blood samples to study the circRNA candidates. The validity of the circRNA candidates as an MPM-specific diagnostic biomarker panel was assessed by applying the ddPCR technique to detect the presence of the circRNA candidates in MPM patient-derived pleural effusion samples. Additionally, the specificity of the circRNA candidates was determined by isolating and measuring the quantity of MPM-specific circulating tumour cells (CTCs) in the patient-derived blood and pleural effusion samples.

**Results:** A bioinformatics analysis revealed that the circRNAs harbor predicted binding sites for tumour suppressor miRNAs: miR-16, miR-15a, miR-15b, miR-34a, miR-34b, miR-34c and miR-137; previously demonstrated to be downregulated in MPM tumour samples and cell lines. We narrowed down our focus to study the candidate circRNAs that were within the top ten of all over-expressed circRNAs, determined from the microarray data. The ddPCR analysis revealed a positive detection for these circRNA candidates in MPM cell lines and were found to be up-regulated when compared to immortalised mesothelial cells. Additionally, the circRNAs were detectable in both Buffy coat and plasma fractions of the patient-derived blood samples.

**Conclusion:** Through the application of the ddPCR technique, the upregulated circRNA candidates were detectable in both MPM cell lines and patient-derived blood samples. Therefore, these circRNA candidates represent potential biomarker candidates for the clinical detection of MPM. Furthermore, as these circRNAs harbor binding sites for a range of tumour suppressor miRNAs, they may also constitute desirable targets for novel treatment strategies.

**Keywords:** biomarker, circular RNA, ddPCR, malignant pleural mesothelioma

---

**MS12.04: Predictive Role of Soluble Levels of PD-L1 in Mesothelioma Patients from the NIBIT-MESO-1 Study**


1Center For Immuno-oncology, Department Of Oncology, University Hospital of Siena, Siena, Italy. 2Breast Cancer Unit, University Hospital of Siena, Siena, Italy

**Parallel Mini-Symposia 12: Management Decisions in Mesothelioma, Virtual, May 9, 2021, 12:30 AM - 2:00 AM**

**Objectives:** Targeting immune checkpoint inhibitors (ICI) significantly improves the overall survival of patients with different tumor types, including pleural mesothelioma; however, no reliable biomarkers predictive of response to treatment have been so far identified. To this end, we investigated changes in circulating levels of soluble PD-L1 (sPD-L1) in mesothelioma patients treated with ICI, their correlation with PD-L1 expression in peripheral, and the potential role of sPD-L1 as predictive biomarker of clinical outcome.

**Methods:** Sera and peripheral blood mononuclear cells (PBMC) were collected from 40 mesothelioma patients treated with the anti-CTLA-4 tremelimumab and the anti-PD-L1 durvalumab within the NIBIT-MESO-1 trial. Changes in circulating levels of sPD-L1 were investigated by ELISA assay, and PD-L1 expression in both CD4 and CD8 T cells by flow cytometry, at baseline and at day 1 of cycle 2 (d1C2), d1C3, d1C5, and d1C8 of therapy. Levels of sPD-L1 were also investigated in sera from additional 82 ICI-treated (i.e., anti-PD-L1, anti-CTLA-4,
anti-PD-1) metastatic lung cancer or melanoma patients in monotherapy or in combination. Mann-Whitney U-test was exploited to study changes in sPD-L1 concentrations between baseline and the different time-points investigated. Ratios of sPD-L1 concentrations at each time-point vs baseline were defined as fold change (FC) values. The best (maximum specificity and sensitivity) cut-off values for concentration and FC of sPD-L1, able to stratify patients according to the overall survival (OS) were determined by ROC curve analyses. Kaplan-Meier analyses were utilized to estimate survival rates, with two-sided 95% CI calculated on the basis of a normal approximation. Survival curves were compared through the log-rank test.

**Results:** Serum levels of sPD-L1 in mesothelioma patients significantly (p<0.001) increased during therapy at all time-points investigated, compared to baseline. The longest OS was observed for patients with sPD-L1 concentrations below the statistically calculated optimal cut-offs, at baseline, C2, and C5 (p=0.004). In addition, patients with a significant (p<0.01) longer OS were those with sPD-L1 FC values higher than the statistically optimal cut-offs calculated at all investigated cycles, except for C8. Consistent with these results, increased levels of sPD-L1 were observed in non-mesothelioma cancer patients treated with anti-PD-L1 agents in monotherapy. Conversely, no significant increase in sPD-L1 serum levels was observed in patients treated with anti-CTLA-4 or anti-PD-1 used alone or in combination. Interestingly, a significant (p<0.0001) decline of PD-L1 positive, CD4 positive or PD-L1 positive, CD8 positive T cell subsets was observed after the first dose of tremelimumab and durvalumab; the latter persisted at all subsequent timepoints investigated. Intriguingly, indirect significant correlations were observed between the decline of PD-L1 expression on both CD4 positive (R2=0.937, p=0.007) and CD8 positive (R2=0.91, p=0.012) T cells and levels of sPD-L1.

**Conclusion:** These results support the specific involvement of ICI treatment with anti-PD-L1 in the release of the sPD-L1, and suggest that sPD-L1 may be a useful predictive biomarker of clinical outcome for mesothelioma patients. Ongoing studies are validating these observations in a larger cohort of cancer patients.

**Keywords:** ICIs, sPD-L1, Biomarker

**MS12.05: Priorities of People With Mesothelioma: A Qualitative Study of Trial Participation and Treatment Decisions**

**Bibby A1, Morley A2, Keenan E2, Maskell N1, Gooberman-Hill R3**

1Bristol Academic Respiratory Unit, Bristol, United Kingdom, 2North Bristol Lung Centre, North Bristol NHS Trust, Bristol, UK, 3NIHR Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, Bristol, UK

**Parallel Mini-Symposia 12: Management Decisions in Mesothelioma, Virtual, May 9, 2021, 12:30 AM - 2:00 AM**

**Background:** Mesothelioma research has expanded dramatically in the past decade, giving patients a wide range of options for participating in trials or receiving new treatments. However, little is known about patients’ and relatives’ priorities when deciding about research. The aim of this study was to characterise the experiences of people with mesothelioma who participated in research to gain insight into the factors influencing their decisions around trials and treatment.

**Methods:** Face to face, semi-structured interviews were undertaken with people with mesothelioma who were participating in ASSESS-meso (a prospective observational cohort study) and in TILT (a randomised feasibility trial of intra-pleural immunotherapy), and their relatives. Patients who declined to participate in the trial were also interviewed. Interviews addressed reasons for taking part or declining and were audio-recorded, transcribed and analysed thematically.

**Results:** Eleven interviews were undertaken with five people with mesothelioma and seven relatives (two of whom were interviewed together). Four main themes were identified: physicality, quality of life, uncertainty and risk, and anxiety and the future.

Participants valued physical strength and many did not wish to jeopardise this with potential side effects from treatments or trial interventions. Quality of life was also important and many people prioritised this over survival when making decisions (Box 1). Anxiety about the future was manifest through concerns about changing symptoms and deteriorating physical function. These
themes were emphasised when participants expressed their preferences for information. Participants expressed a desire for certainty, and wanted information to be delivered as facts or absolutes. This contrasted with the uncertainty about their future and may have been a coping strategy to minimise anxiety. However, the desire for immutable facts sometimes impacted on participants’ ability to assimilate and evaluate risk; important factors when making choices about treatments and trials.

**Conclusion:** This study confirmed previous findings about the value placed on physical strength in people with mesothelioma and highlighted the influence this had on decision-making, alongside quality of life. Communicating risk and achieving informed consent in the context of a desire of certainty means that risk communication needs to be handled with care in this population to ensure that uncertainty is clear and enables evaluation of risk, without compromising coping strategies.

Qualitative research, Patients’ priorities, Research participation, Treatment decisions

"If it was only going to give me two months extra, I wouldn’t have treatment, because the impact of the treatment would affect my quality of life.” M, 81y, patient.

“We’d seen the results of chemo and it didn’t work, it was absolutely hell to go through, so there didn’t seem any point. If you’re not going to get more than a couple of months, what is the point?” F, 71y, wife of patient.

“That first [trial], what I backed out of… I thought, well, with all my ailments another one ain’t gonna be very nice.” M, 74y, patient who declined trial participation.

“I knew that [husband] would say he would help in any way, but when you mentioned this [trial], and he’ll be feeling like he’s got the flu for a while and I thought, ‘Oh, I don’t know... he don’t need any of that.’” F, 72, wife of patient.

Box 1: Quotes highlighting the importance placed on quality of life and the influence of this on treatment decisions and trial participation.
MS12.06: How Much Do We Actually Know Before Embarking on Radical Surgery for Mesothelioma? – the Multidisciplinary Implications for Preoperative Work Up

Baranowski R1, Hargrave J1, Selvaraj A1, Sotiropoulos G1, Waller D1

1St. Bartholomew’s Hospital, London, United Kingdom

Parallel Mini-Symposia 12: Management Decisions in Mesothelioma, Virtual, May 9, 2021, 12:30 AM - 2:00 AM

Objectives: The prognosis following pleurectomy/decortication (P/D) for resectable malignant pleural mesothelioma (MPM) is known to be dependent on histological cell type and nodal metastasis. Preoperative assessment of these parameters may therefore influence treatment selection. We aimed to evaluate the accuracy of preoperative assessment and its effect on postoperative survival after P/D. We aimed to identify possible improvements in preoperative workup.

Methods: P/D or extended P/D was performed in 73 patients: 62 male (85%), 11 female (15%), age 66.8 (33-79) years. All patients were evaluated with non-invasive imaging with CT thorax/abdomen. 23 (32%) also had CTPET. Only 1 patient had invasive mediastinal staging. 56 (78%) had induction chemotherapy and all of these had restaging CT. We recorded discordance between preoperative assessment and postoperative histological findings. We also looked at factors that could predict discordance including the method of biopsy.

Results: Accurate preoperative assessment of both cell type and nodal stage was found in only: 26 of 73 (36%) patients.

Cell type discordance between preoperative assessment and postoperative histology was found in 19 of 73 (26%) patients. In 16 (22%) there was negative discordance (epithelioid to biphasic) whilst 3 (4%) had positive discordance from biphasic to epithelioid. Negative cell type discordance was associated with significantly inferior survival to those with concordant findings (p=0.029)

Cell type discordance was found in 9 of 39 pts (23%) who had a VATS biopsy; 6 of 15 (40%) who had biopsy via medical thoracoscopy and 4 of 18 (22%) who had US/CT guided percutaneous biopsy. The method of biopsy had no significant effect on the rate of discordance (p=0.4).

The effect of maximal tumour thickness on cell type and nodal discordance currently falls below statistical significance.

Nodal discordance was found in 32 of 73 (44%) patients: 24 pts (33%) who were cN0, were pN1 while 8 pts (11%) who were thought to be cN1 were found to be ypN0 (7 patients after induction chemotherapy) and one pN0. Negative nodal discordance was not found to be associated with inferior survival, p=0.72. In the 24 patients with negative nodal discordance (cN0 to pN1) the discordant node/s would have been amenable to EBUS/EUS (i.e stations 2,4,7,8,9,10) in 20 (83%) cases.

We found that overall survival was associated with MPM cell type (epithelioid vs non-epithelioid), p = 0.009, but not with nodal status (pN0 vs pN1), p=0.86.

Conclusion: Clinical assessment before radical surgery should be maximized to improve postoperative survival. Detailed, multiple, multi-site pleural biopsies are needed to reduce cell type inaccuracy. EBUS/EUS nodal biopsies are needed to improve nodal staging based only on imaging. Both cell type and nodal discordance should be noted as a potential confounding factors in the interpretation of comparative survival between surgical and non-surgical modalities.

Keywords: radical surgery, mesothelioma

MS12.07: Mesothelioma in a Developing Country: The Long Path of Patients Inside Health Care Systems to Proper Diagnosis and Management

Gregorio P1, Terra R1, P Lima L1, Martini B1, L Filho R1

1Sao Paulo Cancer Institute - São Paulo University, São Paulo, Brazil

Parallel Mini-Symposia 12: Management Decisions in Mesothelioma, Virtual, May 9, 2021, 12:30 AM - 2:00 AM

Objectives: This study aimed to identify timeframes between critical steps (symptoms, diagnosis, referral to
specialized center, and specific treatment) in disease management and possible elements that may hinder this process.

METHODS: We conducted a retrospective study between 2009 and 2020 analyzing medical records of patients referred to a cancer center. Patients baseline characteristics, history, treatment, procedures, and outcomes were assessed.

RESULTS: During the study period, 70 patients (77% men / 23% women) with a mean age of 60 (±14.6) years old were treated. In the first consultation, 25% of them already had symptoms compatible with an ECOG ≥ 2 and only 45% reported any known exposure to asbestos during their life showing the unawareness related to the risks of this exposure. This finding, together with the fact that patients usually underwent two or more procedures before a definitive diagnostic procedure is made are possible reasons for the long timeframes that patients experience on disease management. The average time between the first symptoms of the disease and referral to a specialized institution was 8.5 months, with an additional 1 month for a conclusive biopsy. Also, patients waited on average more than 1 year between the onset of symptoms and beginning of treatment such as chemotherapy or directed surgery. Around 78% of our patients had stage III or IV disease on initial workup and only in 21% of them pleurectomy/decortication or pleuropneumonectomy could be performed. The overall survival for treated patients was 13.8 months.

CONCLUSIONS: Mesothelioma diagnosis is expected to rise in countries where asbestos regulations have only been adopted recently. Considering that approximately 70% of the mesothelioma cases around the world are associated with asbestos exposure, and the fact that less than a half of our sample have a known exposure, our findings suggest the current impact of this unawareness. Also, the unfamiliarity of physicians with the disease may result in an extended period of time before patients are properly managed what certainly impacts their prognosis.

Asbestos, Pleura, Mesothelioma, Epidemiology

MS13.02: Assessment of Apparent Diffusion Coefficient in Biphasic Malignant Pleural Mesothelioma from Diffusion Weighted MRI (DWI)

Gill R1, Bueno R2, Seethamraju R3, Chirieac L4, Richards W2

1Department of Radiology, Beth Israel Deaconess Medical Center, Boston, USA, 2Department of Surgery, Brigham and Women’s Hospital, Harvard Medical School, Boston, USA, 3Siemens Healthineers, , 333 Coney St, East Walpole, , USA, 4Department of Pathology, Brigham and Women’s Hospital, Harvard Medical School, , Boston, USA, 5Department of Surgery, Brigham and Women’s Hospital, Harvard Medical School, , Boston, USA

Parallel Mini-Symposia 13: Imaging, Virtual, May 9, 2021, 12:30 AM - 2:00 AM

Objectives: We have previously shown that Diffusion weighted MR imaging can be used to predict histological types in Malignant Pleural Mesothelioma (Gill et al AJR 2010). We assessed whether apparent diffusion coefficient (ADC) values derived from free-breathing single-shot spin-echo echo-planar imaging sequences can be used to identify the predominant component within biphasic tumors.

Methods: Preoperative MRI was performed on a 3-T MRI. Axial DWI images were acquired with fat suppression and free breathing single shot spin echo EPI sequence (4000/84); section thickness, 8 mm, interslice gap, 1.5 mm, number of signals averaged 6; field of view 400mm, matrix size 160x 96; b value 50, 250, 500 and 750 s/mm² for three orthogonal diffusion directions, Apparent diffusion coefficient maps were generated. The pathologic diagnosis was confirmed in surgical pathology specimens from biopsies or resections. Qualitative assessment of the ADC maps was also done and categorized into 3 categories-optimal, marginal and suboptimal. The mean ADC of the tumor was calculated by placing 10 regions of interest over the ADC map after carefully selecting areas of tumor on the post contrast VIBE images. ADC values were compared using the Pearson’s correlation .

Results: The study cohort comprised of 98 Biphasic MPM’s; 60 (61%) epithelioid predominant (BE) and 38 (39%) sarcomatoid predominant (BS). Forty-five (46%) patients underwent extrapleural pneumonectomy (EPP), 49(50%) Pleural decortication (PDC) and 4 (4%) Pleural
biopsies. The tumor volume was 33-2159 cm³. Clinical AJCC Stage was I in 10 (10%); II in 41 (42%), III in 35 (36%) and IV in 12 (12%) patients. The ADC values ranged between 696 x 10⁻⁶ to 1921 x 10⁻⁶ mm²/s.

(Fig 1) Moderate linear correlation between ADC values and tumor volume. There was an overlap of ADC values between both groups with no clear cut-off value to differentiate the two groups (BE and BS), however, when stratified by tumor volume at the median tumor volume of 583 cm³ it was possible to separate the smaller volume tumors based on the predominant component but not in the larger tumors by ADC values (p = 0.0006). (Fig 2)

**Conclusion:** ADC values derived from DWI may have prognostic significance but has limited predictive potential in differentiating the predominant subcomponent among patients with Biphasic Malignant Pleural Mesothelioma.

**Keywords:** MPM, DWI, MRI, ADC, Biphasic mesothelioma
**MS13.03: A Comparison of Magnetic Resonance and Computed Tomography Imaging for Measurement of Primary Tumour Volume in Mesothelioma**

Tsim S1, Cowell G3, Kidd A3, Woodward R4, Alexander L5, Kelly C5, Foster J4, Blyth K1,3

1Glasgow Pleural Disease Unit, Queen Elizabeth University Hospital, Glasgow, United Kingdom, 2Department of Radiology, Queen Elizabeth University Hospital, Glasgow, United Kingdom, 3Institute of Cancer Sciences, University Of Glasgow, Glasgow, United Kingdom, 4Clinical Research Imaging Facility, Queen Elizabeth University Hospital, Glasgow, United Kingdom, 5Cancer Research UK Clinical Trials Unit Glasgow, Institute of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom

**Parallel Mini-Symposia 13: Imaging, Virtual, May 9, 2021, 12:30 AM - 2:00 AM**

**Objectives:** Primary tumour staging in Malignant Pleural Mesothelioma (MPM) using Computed Tomography (CT) imaging is confounded by perception errors reflecting low tumour contrast with adjacent structures. Augmentation using perfusion CT is constrained by radiation dosage. In this study, we evaluated an alternative tumour staging method using perfusion-tuned Magnetic Resonance Imaging (MRI).
**Methods:** Consecutive patients with suspected MPM were recruited to a prospective observational study. All had MRI (T1-weighted, isotropic, contrast-enhanced 3-Tesla perfusion imaging) and CT (contrast-enhanced) pre-biopsy. Patients diagnosed with MPM underwent blinded MRI and CT volumetry. MRI volumetry was semi-automated, using signal intensity limits from perfusion studies to grow tumour regions within a pleural volume. A similar CT method was not possible, therefore all visible tumour was manually segmented. MRI and CT volumes were compared (agreement, correlation, analysis time, reproducibility) and associations with survival examined using Cox regression.

**Results:** 31/66 patients had MPM and underwent volumetry. Mean (SD) MRI and CT volumes were 370cm³ and 302cm³, respectively. MRI volumes were larger (average bias 61.9 (SD 116), 95% limits (-165.5 - 289), moderately correlated with CT (r=0.56, p=0.002) and independently associated with survival (HR 2.11 (95% CI 1.05 – 4.27, p=0.037), see Figure 1. CT volume was not associated with survival, took longer than MRI (mean (SD) 151 (19) v 14 minutes (2), p=<0.0001) and was less reproducible (inter-observer ICC 0.72 for CT, 0.96 for MRI), see Figure 2.

**Conclusion:** MRI and CT generate different tumour volumes in MPM. MRI volumes were larger and independently associated with survival. MRI volumetry was quicker and more reproducible than CT.

**Keywords:** Mesothelioma MRI CT Volumetry Staging Prognosis
**MS13.05: TARGET TRIAL - A Randomised Controlled Trial to Compare the Diagnostic Yield of PET-CT TARGETed Pleural Biopsy Versus CT-guided Pleural Biopsy in Suspected Pleural Malignancy**

de Fonseka D¹, Maskell N²

¹Academic Respiratory Unit, University Of Bristol, Bristol, United Kingdom, ²Academic Respiratory Unit, University Of Bristol, Bristol, united kingdom

Parallel Mini-Symposia 13: Imaging, Virtual, May 9, 2021, 12:30 AM - 2:00 AM

**Objectives:** Obtaining a histological diagnosis of pleural malignancy can be challenging, especially in cases of mesothelioma. A small subset of individuals have a non-diagnostic initial biopsy and require further interventions. This leads to treatment delays, and is more invasive and distressing for the patient. The TARGET trial was set up to investigate the role of PET-CT targeted biopsies in this population of patients with one non-diagnostic biopsy.

**Methods:** TARGET is a prospective multi-centre randomised controlled trial funded by the National Institute for Health Research UK (PB-PG-0214-33095). Patients were recruited from 10 sites in the UK. Patients with 1 non-diagnostic pleural biopsy who required a further CT guided biopsy, were randomised to either the standard arm; a second CT guided biopsy, or the interventional arm; a PET-CT scan followed by a targeted CT guided biopsy. Patients were then followed up for 12 months from randomisation. Mesothelioma biomarker Mesothelin was checked at baseline, 6-month and 12-month follow-up appointments.

**Results:** Fifty-eight patients were recruited from 10 sites across the UK, from 09/2015 to 09/2018. The follow up period is complete, statistical analysis plan signed off and database locked. The analysed data will be available for presentation at the iMig 2020 meeting.

**Conclusion:** The results from this trial will hopefully demonstrate whether there is an added benefit to performing PET scans in patients with suspected pleural malignancy, who have had a non-diagnostic pleural biopsy.

**Keywords:** mesothelioma, pleural mesothelioma, PET-CT, biopsy, pleural malignancy

**MS13.06: Measurement Methods and Patient Outcomes in Malignant Pleural Mesothelioma**

Kholmatov M¹, Li F¹, Qayyum F¹, Kindler H¹, Armato III S¹

¹University of Chicago, Chicago, United States

Parallel Mini-Symposia 13: Imaging, Virtual, May 9, 2021, 12:30 AM - 2:00 AM

**Objectives:** Change in tumor size as a percentage of baseline disease burden is the current basis for assessing patient response to cancer therapy. In patients with malignant pleural mesothelioma (MPM), baseline disease burden and the change from baseline are determined by the mRECIST 1.1 criteria, which recommend measurement of up to 6 sites of disease above 7 mm in thickness. Altering the number or size threshold of measurement sites on baseline and follow-up scans could impact the assessed patient response. The objective of this study was to determine the impact of changes in these parameters on patient response and to evaluate whether any single measurement approach best correlated with patient survival.

**Methods:** Computed tomography (CT) scans from 72 patients with MPM enrolled in two clinical trials were collected. Tumor thickness was measured at exactly 6 sites by an experienced chest radiologist. Measurement approaches (12 total) that varied the number of sites (6, 5, 3, 2, 1 sites) and the size threshold (10 mm, 7 mm, 5 mm, 0 mm), including the mRECIST 1.1 clinical standard, were implemented to calculate a summed tumor measurement for each scan. Changes in summed tumor measurements were used to obtain the response derived from each measurement approach for (1) each patient follow-up scan and (2) overall best response; best responses then were correlated with patient survival to assess the clinical utility of these approaches.

**Results:** Patient response derived from the various measurement approaches differed from the clinical standard response in as many as 29.3% of follow-up scans (mean 21.9%) and 27.8% (mean 17.16%) of best responses. 9.1% of follow-up scan responses were considered progressive disease (PD) in the clinical standard approach but classified...
as stable disease (SD) using other approaches, and 10.4% of best responses considered PD in the clinical standard approach were considered SD using other approaches. Some approaches using reduced thresholds of measurable disease achieved improved correlation with survival compared with the current clinical standard. For example, the approach using 6 measurements ≥ 5 mm achieved a C-value of 0.56 (p = 0.05), while the current clinical standard achieved a C-value of 0.46 (p = 0.21).

Conclusion: Changes in the number of measurement sites selected and the threshold for minimally measurable disease resulted in differences in patient response classification, and approaches that used a smaller threshold for measurable disease yielded response classifications that correlated better with patient survival than did those derived from the clinical standard.

Mesothelioma, tumor measurement, tumor response assessment, modified RECIST

**MS13.07: Prognostic Significance of Loss of Skeletal Muscle in Patients with Malignant Pleural Mesothelioma Receiving Chemotherapy**

Kidd A¹, Winter A³, Miller L³, Baird W³, Dick C⁴, Pearce D³, Sloan W³, Cowell G⁵, Noble C¹, Smith A³, Westwood P³, Hopkins T⁶, Williams N⁷, Walter H⁹, King A⁹, Fennell D⁹, Blyth K²

¹Institute of Immunity, Infection and Inflammation, University Of Glasgow, Glasgow, United Kingdom, ²Glasgow Pleural Disease Unit, Queen Elizabeth University Hospital, Glasgow, United Kingdom, ³Molecular Pathology, Queen Elizabeth University Hospital, Glasgow, United Kingdom, ⁴Pathology, Queen Elizabeth University Hospital, Glasgow, United Kingdom, ⁵Bioinformatics, Fios Genomics, Edinburgh, United Kingdom, ⁶Radiology, Queen Elizabeth University Hospital, Glasgow, United Kingdom, ⁷Radiology, Glasgow Royal Infirmary, Glasgow, United Kingdom, ⁸Glasgow Clinical Research Facility, NHS Greater Glasgow & Clyde, Glasgow, United Kingdom, ⁹Cancer Research UK Centre Leicester, University of Leicester, Leicester, United Kingdom

Parallel Mini-Symposia 13: Imaging, Virtual, May 9, 2021, 12:30 AM - 2:00 AM

Objectives: There are very few studies describing the prevalence of sarcopenia or factors associated with loss of skeletal muscle in patients with Malignant Pleural Mesothelioma (MPM). We determined the prognostic implication of loss of skeletal muscle between pre-chemotherapy and response assessment in patients with MPM who received platinum-pemetrexed chemotherapy within the PRiSM (Prediction of Resistance to chemotherapy using Somatic Copy Number Variation in Mesothelioma) study, which is funded by the British Lung Foundation.

Methods: Baseline clinical information was collected regarding 113 patients with MPM who received chemotherapy in the West of Scotland between 2008 and 2017, and have been selected for inclusion in PRiSM. Patients were eligible for the current study if the body composition analysis could be performed on a single image at the third lumbar vertebrae (L3) on Computed Tomography (CT) scans. Patients were excluded if their CT imaging did not extend inferior enough to include L3.

Body composition analysis used established Hounsfield Unit thresholds and ImageJ software (National Institutes of Health, Bethesda, MD, USA). Patients were dichotomised into those exhibiting any loss of skeletal muscle (defined as a decrease in skeletal muscle index >= 0.5 cm²/m²) between pre-chemotherapy and response assessment CT scans, and those not exhibiting this. Overall survival (OS) was generated using the Kaplan-Meier method and compared using the log-rank test. Differences in baseline characteristics, including age, histological sub-type and circulating measures of systemic inflammation were compared using chi-squared tests.

Results: 70/113 eligible patients were included, based on available L3 imaging. 37/70 patients lost skeletal muscle between baseline and response assessment CT scans. The median OS was 447 days (CI 261–486) in those losing skeletal muscle and 774 (CI 442–695) days in those not (p=0.046), Figure 1). The neutrophil: lymphocyte ratio (NLR) was higher in patients exhibiting skeletal muscle loss on chemotherapy (up=0.049).

Conclusion: In this small study, loss of skeletal muscle between pre-chemotherapy and response assessment CT scans was prognostically significant and was associated with higher levels of systemic inflammation pre-chemotherapy. Further larger studies are warranted since sarcopenia may be a predictable and reversible form of chemotherapy toxicity.

Keywords: Malignant Pleural Mesothelioma, Sarcopenia, Imaging
MS13.08: Texture Analysis for the Differentiation of Malignant Pleural Mesothelioma Histologic Subtypes on CT Scans

Gudmundsson E1, Chapel D1, Straus C1, Li F1, Kindler H1, Husain A1, Armato S1

1University Of Chicago, Chicago, United States

Parallel Mini-Symposia 13: Imaging, Virtual, May 9, 2021, 12:30 AM - 2:00 AM

Objectives: Tumor histologic subtype is the most significant prognostic factor in malignant pleural mesothelioma (MPM), with the epithelioid subtype carrying a significantly better prognosis than the biphasic and sarcomatoid subtypes. Texture analysis is a computerized method that employs mathematical “texture features” calculated from medical images to quantify clinically relevant tumor characteristics. The aim of this study was to investigate the use of texture analysis of computed tomography (CT) scans for the non-invasive image-based differentiation of MPM tumor histologic subtypes.

Methods: 81 MPM patients were retrospectively collected for this study; a single CT scan of each patient was included in the analysis. Study exclusion criteria included the lack of a CT scan prior to surgical resection or prior to talc pleurodesis, significant fluid component of tumor, insufficient tumor size for analysis, and chest wall invasion. 37 of the tumors analyzed in this study were of epithelioid histology, 33 tumors were biphasic, and 11 tumors were of the sarcomatoid subtype. All epithelioid and biphasic tumors included in this study were diagnosed based on surgical tumor resection; 9 out of 11 sarcomatoid tumors were diagnosed by pleural biopsy. Tumor outlines were constructed on a single CT section showing the largest cross-sectional extent of tumor; all outlines were reviewed by a thoracic radiologist. 31 texture features were calculated based on the pixel values within the outlined tumor of each scan. Texture feature values were used to train a logistic regression model to classify tumors as “epithelioid” and “non-epithelioid” (i.e., sarcomatoid or biphasic histology). Receiver operating characteristic (ROC) analysis was used to assess the overall specificity and sensitivity of the classification model.

Results: Figure 1 shows a histogram of classifier scores for the differentiation of epithelioid and non-epithelioid tumors for the 81 patients collected for this study. The area under the ROC curve for the classifier was 0.67 +/- 0.06 with a 95% confidence interval of [0.54, 0.77], which indicates an overall discrimination performance statistically significantly different from classification by chance alone.
Conclusion: Texture analysis was used to develop a logistic regression model for the non-invasive differentiation of epithelioid and non-epithelioid MPM tumor on CT scans. The resulting model achieved a classification performance significantly different from that by chance alone. Limitations of this study include the retrospective nature of the analysis and the small number of patients included in the study.

Keywords: malignant pleural mesothelioma computed tomography image analysis texture features histology

PL04.05: Synergic Immunomodulating Antitumor Effect of IL-15 Superagonist and GITR Agonist After Local Non-ablative Hypofractionated Radiotherapy in Mesothelioma

Murakami J1, Wu L1, Kohno M1, Chan M1, Zhao Y1, Yun Z1, de Perrot M1

1Latner Thoracic Surgery Research Laboratories, UHN, Toronto, Canada

Plenary IV: Immunotherapy - Checkpoint Blockade and Beyond, Virtual, May 9, 2021, 2:00 AM - 3:30 AM

Objectives: Preclinical studies demonstrate that local radiotherapy (LRT) generates a more immunogenic tumor microenvironment. We previously demonstrated that non-ablative hypofractionated LRT potentiates immune-stimulatory effects (antigen-specific immunity and in situ vaccination mediated by memory T cells) in murine models of mesothelioma. However, the immune-stimulatory responses are limited by the upregulation of regulatory CD4+ CD25+ Foxp3+ T cells (Tregs) into the tumor. We explored the possibility to improve the local and systemic immunogenic effects of LRT by increasing the upregulation of cytotoxic cells with IL-15 superagonist (IL-15SA) and depleting Tregs with agonistic anti-GITR mAb (DTA-1). DTA-1 can engage with GITR on Tregs and impair their immunosuppressive activity by hyperactivation and depletion of Tregs.

Methods: C57BL/6 mice bearing subcutaneous AE17-OVA tumor were treated with LRT using 15 Gy in 3 daily fractions. IL-15SA and DTA-1 were systemically administered as monotherapy or in combination to tumor-bearing mice treated with LRT. In addition, a dual subcutaneous tumor-bearing model was used to determine the abscopal effect of LRT delivered to the primary tumor with systemic IL-15SA and DTA-1 followed by resection of the primary tumor.

Results: Kinetic studies confirmed that LRT remarkably increased CD8+ T cells and Tregs infiltration into the tumor. Tregs accumulated before CD8+ T cells and expressed a much higher level of GITR (98% GITR+) than Tregs in lymph nodes and spleen (70% GITR+), as well as CD8+ and Foxp3-CD4+ T cells in the tumor (37% and 45% GITR+, respectively). In addition, there was a spike of M1 macrophages (CD11b+F4/80+Ly6G-Cd206-) and inflammatory monocytes (CD11b+Ly6ChighLy6G-) into the tumor on the first day after LRT. IL-15SA expanded NK cells and CD8+ T cells, and potently increased central and effector memory (CD44+CD62L+ and CD44+CD62L-) T cell subsets with antigen-specific cytotoxicity against the tumor. DTA-1 efficiently depleted GITR+ Tregs in the tumor. DTA-1 did not deplete Tregs in the spleen and lymph nodes. Both IL-15SA and DTA-1 alone had an impact on tumor growth after LRT. However, combination therapy (IL-15SA/DTA-1) synergistically inhibited tumor growth after LRT. These findings were reproduced in Balb/c mice with AB12 mesothelioma. Tumor regression was characterized by increased OVA-specific CD8+ T cell infiltration and increased ratio of CD8+ over Treg tumor-infiltrating lymphocytes. This was associated with the up-regulation of CD69, IFN-γ, TNF-α, and Gzm-B on CD8+ T cells in draining lymph nodes. In the dual tumor model, radio-immunotherapy significantly slowed the growth of the secondary tumor when IL-15SA and DTA-1 were conjointly administered before resecting the primary tumor.

Conclusion: Combination IL-15 superagonist and agonistic anti-GITR mAb showed synergistic antitumor effects, and induced abscopal response after non-ablative hypofractionated LRT in our preclinical murine models of mesothelioma. Thus, radio-immunotherapy followed by surgery could be an effective approach for patients with resectable mesothelioma. The abscopal effect generated by radio-immunotherapy could be an efficient way to control residual micrometastasis after macroscopic complete resection. Our findings support further exploration of this combination therapy with LRT in the clinical setting.
**PL04.06: Dynamic Changes in T Cell Receptor Diversity Correlate with Successful Responses to Immune Checkpoint Blockade Outcomes in Murine Mesothelioma**

**Kidman J¹, Principe N¹, Zemek R², Chin M¹, Forbes C², Fear V¹, Chopra A², Fisher S¹, Zaitouny A³, De Jong E¹, Correa D⁵, Holt R⁴, Nowak A¹, Watson M⁵, Lassmann T², Lake R¹, Lesterhuis W¹,², Chee J¹**

¹University of Western Australia, National Centre For Asbestos Related Diseases, Perth, Australia, ²Telethon Kids Institute, Perth, Australia, ³Murdoch University, Institute for Immunology and Infectious Diseases, Perth, Australia, ⁴British Columbia Cancer Genome Center, Vancouver, Canada, ⁵University of Western Australia, Department of Mathematics, Complex Systems, Perth, Australia

**Plenary IV: Immunotherapy - Checkpoint Blockade and Beyond, Virtual, May 9, 2021, 2:00 AM - 3:30 AM**

**Objectives:** Checkpoint blockade immunotherapy (CPB) is approved for treatment in several cancers and is currently being tested in mesothelioma. Whilst some treated patients experience long-term tumour regression, only a minority of treated patients respond to CPB. Profiling immune changes in responders and non-responders to CPB provides crucial mechanistic insight that will guide the development of treatment biomarkers, and new therapies. T cells are a primary effector cell that mediate anti-cancer immune responses. Our study profiles T cell repertoires of responding and non-responding murine mesothelioma tumours to CPB with T cell receptor beta (TCRβ) sequencing. We hypothesize that differential dynamics of the TCRβ repertoire, such as clonal expansion and TCRβ connectivity, define CPB responses.

**Methods:** We utilised an established bilateral, transplantable tumour model which controlled variation in host genetics and tumour antigen expression. In this model, bilateral mesothelioma (AB1) tumours either grow or regress symmetrically following treatment with checkpoint blockade immunotherapy (CPB) (anti-CTLA4 + anti-PD-L1). These results were confirmed in independent experiments using a renal cell carcinoma (RENC) tumour model. A source of variation comes from the naturally diverse TCRβ repertoire found between animals, allowing us to measure the TCRβ repertoire’s contribution to CPB outcome. Furthermore, the symmetry of response allows for excision of one tumour as a readout for immune status, whilst leaving the other as a readout for CPB outcome. Tumours were sampled at four time points: one hour prior to CPB, or 2, 4 or 6 days after. We sequenced the excised tumours, and profiled clonal expansion of distinct TCRβ clonotypes. Distinct TCRβ clones cannot be directly compared so we developed a novel pipeline to cluster TCRβ sequences based on amino acid similarity using Hidden Markov Models (HMM) seeded by a greedy clustering alignment algorithm.

**Results:** Although responding and non-responding animals exhibited reduction in TCR diversity and clonal expansion in their tumour TCRβ repertoires, a key difference was that clonal expansion occurred early on-treatment in responders; while this eventually also occurred in non-responders, this was much later. Interestingly, each mouse selectively expanded private TCRβ clonotypes, with minimal sharing between animals regardless of response. Next, we examined if there were features of TCRβ sequences, such as common amino acid motifs that were informative for treatment outcomes and tumour specificity. Our novel pipeline clustered TCRβ sequences based on amino acid edit distance, and clearly delineated different tumour models, suggesting the computational pipeline identifies biologically meaningful differences in TCRβ repertoire. We further identified clusters that were over-expressed in responding tumours compared to non-responding tumours, identifying a key feature of anti-cancer T cell proliferation that predicts response before measurable differences in tumour size.

**Conclusion:** TCR diversity dynamics distinguish murine mesothelioma responses to checkpoint blockade therapy before there is a detectable difference in tumour size. We propose that our approach effectively represents intratumoural T cell proliferation and detects subtle differences early in treatment that determine response.
**ABSTRACTS**

**PL05.05: A Safety Study of Avelumab plus SBRT in Malignant Mesothelioma**

*Rimner A*¹, Yorke E¹, Gelblum D¹, Shepherd A¹, Guttmann D¹, Iqbal A¹, Daly R¹, Offin M¹, Fiore J¹, Namakdyoust A¹, Li H¹, McCune M¹, Gelb E¹, Taunk N¹, von Reibnitz D¹, Adusumilli P¹, Rusch V¹, Zauderer M¹

¹Mskcc, New York, United States

**Plenary V: Cutting Edge 2020, Virtual, May 9, 2021, 1:00 PM - 2:30 PM**

**Objectives:** Single-agent anti-PD-L1 therapy has shown modest effects in mesothelioma. There is evidence that radiation therapy can enhance the anti-tumor effects of immunotherapy. However, the safety of combining anti-PD-L1 therapy specifically with stereotactic body radiation therapy is unknown. This is a phase I study to evaluate the safety of the anti-PD-L1 monoclonal antibody avelumab plus SBRT in malignant pleural and peritoneal mesothelioma. This is a clinical trial in progress report on the safety data of the first stage of this trial.

**Methods:** This is a single-arm, single-institution study in patients who have progressed after prior therapy. Baseline biopsies are obtained for histologic confirmation of progressive disease. Avelumab is delivered every other week and SBRT to one lesion is delivered over 3 to 5 fractions (minimum of 30 Gy) followed by continuation of avelumab up to 24 months or until disease progression. A second research biopsy of the radiation target lesion and a non-irradiated lesion is performed after completion of 2 doses of avelumab and SBRT. The primary endpoint of the study is the safety of this combination based on grade 3+ non-hematologic adverse events (AE) (CTCAE v4.0) within 3 months form SBRT using a Simon two-stage minimax design. If less than 3 of the first 13 patients experienced grade 3+ toxicity, the treatment would be considered safe and the trial will expand to include an additional 14 patients.

**Results:** Patients received a median of 7 cycles (range 2 to 26 cycles) of avelumab for a median duration of 3.5 months. With a median follow up of 4 months there were 13 grade 1, 11 grade 2 and one grade 3 AEs observed that were possibly related to avelumab. There were no grade 4 or 5 toxicities related to avelumab. The most common avelumab-related toxicities were fatigue (n=4), infusion-related allergic reactions (n=3), myalgia/arthritis (n=3), diarrhea (n=2), dyspnea (n=2) and thyroid disorders (n=2). There were 7 grade 1 and 3 grade 2 AEs observed that were possibly related to SBRT. There were no grade 3, 4 or 5 toxicities related to SBRT. The most common SBRT-related toxicities were fatigue (n=2), cough (n=2), dyspnea (n=2) and nausea/vomiting (n=2).

**Conclusion:** The combination of avelumab and SBRT appears safe based on the prespecified toxicity endpoints of the first stage of this Simon two-stage design phase I study. Patients continue to be monitored for long-term toxicities.

**PL05.06: 3D Mesothelioma Co-culture Models to Evaluate Innovative Anti-tumor Immunotherapies**

Blondy T¹, Grard M¹, Briolay T¹, Petithomme T¹, Deshayes S¹, Grégoire M¹, Boisgerault N¹, Fonteneau J¹, Blanquart C¹

¹Université de Nantes, Inserm, CRCINA, F-44000 Nantes, France, Nantes, France

**Plenary V: Cutting Edge 2020, Virtual, May 9, 2021, 1:00 PM - 2:30 PM**

**Objectives:** Pre-clinical evaluation of the efficacy of new immunotherapeutic strategies mainly relies on the use of classical 2D culture systems combined to artificial animal models that incompletely recapitulate the human clinical situation. New complex culture systems are currently being developed to facilitate the study of the human tumor microenvironment, to test new therapies and to better understand how different cell types respond to those. Additionally, such models could be an alternative or complementary to the use of animals in medical research. Here, we sought to determine whether MultiCellular Tumor Spheroids (MCTS) of malignant pleural mesothelioma (MPM) cells could be used to study the mechanisms at play when treating malignant and tumor-associated cells with different novel immunotherapies.

**Methods:** MCTS were established by using human MPM cell lines, from a former described biocollection, co-cultured in non-adherent conditions with human macrophages, fibroblasts or both. When the MCTS were formed, they were analyzed for their structure and content up to 10 days. They were subsequently treated following two protocols. In protocol 1, a human MUC1-specific CD8 T cell clone was added on the MCTS to test its cytotoxicity...
in presence or not of the anti-PD1 antibody nivolumab. In a second protocol, the MCTS were infected by oncolytic strains of both Measles Virus (MV) and Vesicular Stomatitis Virus (VSV) and tumor cell lysis was analyzed for several days.

**Results:** The presence of macrophages and fibroblasts in these MCTS allowed us to recapitulate the immunosuppression commonly observed in the tumor microenvironment as macrophages acquired an ‘M2-like’ phenotype when in contact with malignant cells. When using the first treatment, we observed that the activity of the MUC1-specific T cell clone was dramatically lessened in the presence of these immunosuppressive macrophages and fibroblasts but that nivolumab restored T cell activity and led to extensive T cell-dependent tumor cell killing depending on MCTS constitution. In the oncolytic virotherapy protocol, the presence of non-malignant cells limited the propagation of the viral infection compared to spheroids made of tumor cells only. We found that the type I interferon response from the healthy cells was responsible for this effect as the use of the JAK/STAT inhibitor Ruxolitinib restored efficient infection of tumor cells by both oncolytic viruses.

**Conclusion:** MCTS and other 3D culture systems are new alternatives to recreate in vitro certain features of the human tumor microenvironment. These can be used to rapidly evaluate the efficacy of novel therapies and to study the biological mechanisms at play in the human setting. Further refinements of these systems, such as the addition of endothelial cells or other types of immune cells, will make them even more relevant in the future and could help to limit the use of artificial animal models such as tumor xenografts and other immunodeficient tumor models.

**Models, immunotherapy, virotherapy, macrophages, immunology, oncolytic, virus, PD-1, T cell**

**MS14.04: BAP1 Loss Predicts Therapeutic Vulnerability in Malignant Peritoneal Mesothelioma**


¹Vancouver Prostate Centre, Vancouver, Canada, ²University of British Columbia, Vancouver, Canada, ³British Columbia Cancer Agency, Vancouver, Canada, ⁴Mount Sinai Hospital, Toronto, Canada, ⁵Moores Cancer Center, La Jolla, United States, ⁶Vancouver General Hospital, Vancouver, Canada

**Objectives:** Malignant Peritoneal Mesothelioma (PeM) is a rare but frequently fatal cancer that originates from the peritoneal lining of the abdomen. Standard treatment of PeM is limited to cytoreductive surgery and/or chemotherapy, and no effective targeted therapies for PeM yet exist. Moreover, distinct molecular alterations responsible for its aggressiveness are not well defined.

**Methods:** In the search for novel therapeutic target candidates in PeM, we performed a comprehensive and integrative multi-omics characterization of 19 fresh-frozen primary treatment naïve PeM tumors from patients who underwent cytoreductive surgery. The PeM tumors and their adjacent benign tissues were subjected to whole exome/transcriptome sequencing and mass spectrometry. We assessed the somatic mutation, copy-number aberration, gene-fusions, gene and protein expression using standard bioinformatics tools. We integrated these multi-omics data using our recently developed computational algorithm - HIT’nDRIVE. Briefly, HIT’nDRIVE measures the potential impact of genomic aberrations on changes in the global expression of other genes/proteins which are in close proximity in a gene/protein-interaction network. It then prioritizes aberrations with the highest impact as cancer driver genes. Furthermore, we have established patient-derived xenografts (PDX) models by orthotopically implanting live tumors onto the subrenal capsule of SCID/NOD mice in which we can further test the therapeutic efficacy of promising drug candidates.
**Results:** The mutation and copy-number landscape of PeM is highly heterogeneous and quite as compared to other cancer types. Multi-omics data integration of the genomes, transcriptomes, and proteomes using HIT’nDRIVE revealed loss of genes in chromosome 3p21 as a key driver event in PeM. Interestingly, we found DNA copy loss of this locus to include four cancer genes - BAP1, SETD2, SMARCC1, and PBRM1, in about 40% of PeM tumors. Here, we demonstrate that PeM with 3p21 loss (BAP1del) forms a distinct molecular subtype markedly different from tumors with 3p21 intact (BAP1intact). Transcriptome and proteome profiles revealed distinct set of signaling pathways dysregulated between the two PeM subtypes. Notably, the BAP1del subtype is characterized by distinct expression patterns of genes involved in chromatin remodeling, DNA repair pathway, and immune checkpoint receptor activation. This PeM subtype could potentially benefit from immune checkpoint, PARP, or HDAC inhibition therapies. Moreover, we found the BAP1del subtype has tumor infiltrated leukocytes suggesting potential use of immune-checkpoint blockade for these tumors. Furthermore, our integrative analysis revealed that expression patterns of chromatin modifier protein complexes such as – SWI/SNF, HDAC complexes differ between the PeM subtypes. We found that in these different multimeric complexes, the effects of copy-number aberration on protein abundance are counterbalanced by post-transcriptional modifications to maintain functional stoichiometry.

**Conclusion:** Our first-in-field multi-omics data reveal that PeM tumors with BAP1 loss is a distinct molecular subtype that can potentially be targeted with PRAP, HDAC, or immune-checkpoint inhibitors. If validated this suggests that almost half of PeM patients may benefit from these therapies. Our findings identify BAP1 as a trackable prognostic biomarker, and refine PeM disease classification.
BRCA1/2 mutagenesis was clonally enriched in 13 patients (52%). Clonal BAP1, BRCA1 and BRCA2 mutations were present in these tumours. Subclonal sig3 enrichment was seen in 4 patients (16%). Two patients exhibited both clonal and subclonal sig3.

Knock out of BAP1 in a HAP1 model conferred significantly increased DNA damage levels to the PARP inhibitor, rucaparib, measured by Comet assay. Rucaparib sensitivity correlated with copy number variation of DDR genes including MRE11A, NBN, RAD51C, RAD51D, FANCD2, FANCM, FANCC, BRIP1 and CDK12. Explants treated with rucparib in the MEDUSA cohort exhibited differential sensitivity, with one sensitive tumour harbouring clonal sig3 and BRCA2 mutation. Sequencing and correlation with rucaparib sensitivity in the MIST1 trial is ongoing.

**Conclusions:** Mesotheliomas harbour numerous early clonal DDR somatic alterations that may confer PARP inhibitor sensitivity and could potentially improve the precision of PARP inhibitor stratification.

**Keywords:** BAP1, homologous recombination deficiency, PARP inhibitor, signature 3, DNA damage


**Keywords:** BAP1, homologous recombination deficiency, PARP inhibitor, mutational signature 3

**MS14.06: Transglutaminase 2 Enhances Hepatocyte Growth Factor Signaling To Drive the Mesothelioma Cancer Cell Phenotype**

**Naselsky W**1, Adhikary G1, Shresha S1, Xu W1, Friedberg J1, Eckert R1

1University of Maryland School of Medicine, Baltimore, United States

**Objective:** Mesothelioma is an aggressive cancer that has a poor prognosis. Tumors develop in the mesothelial lining of the pleural and peritoneal cavities in response to asbestos exposure. Surgical debulking followed by chemotherapy is initially effective, but this treatment ultimately selects for resistant cells that form aggressive and therapy resistant recurrent tumors. Transglutaminase 2 (TG2) is a mesothelioma cancer cell (MCS cell) maintenance and survival protein. Our objective is to understand how TG2 drives mesothelioma cancer stem cell (MCS cell) survival and to determine if TG2 can serve as a therapy target.

**Methods:** Mesothelioma cancer stem cells (MCS cells) are a highly aggressive subpopulation present in tumors that are responsible for tumor maintenance and drug resistance. In the present manuscript, we use transcriptomics analysis, cell culture, TG2 knockdown and CRISPR/Cas9-mediated knockout, TG2 inhibitor treatment, tumor formation, and biochemical signal transduction analysis methods to examine the impact of targeting TG2 on the MCS cell phenotype.

**Results:** We show that TG2 drives hepatocyte growth factor (HGF) signaling to maintain aggressive MCS cell and non-stem cell cancer cell phenotypes. TG2 knockdown, CRISPR knockout or inactivation using a specific inhibitor reduces HGF-receptor MET tyrosine kinase activity, and MEK1/2 and ERK1/2 activity leading to reduced MCS cell spheroid formation, invasion, and migration. Moreover, inhibition of MEK1/2 or ERK1/2 phenocopies that response to the TG2 inhibitor. Additionally, MET-knockout reduces MET, MEK1/2 and ERK1/2 activity in tumors, doubles the time required for tumor formation and results in slower overall tumor growth. Similar results are observed for both pleural and peritoneal mesothelioma.

**Conclusion:** We propose that TG2 maintains an HGF/MET, MEK1/2, ERK1/2 signaling cascade that drives aggressive MCS cell tumor formation. The fact that TG2 activates HGF/MET, and a range of other synergizing signaling cascades involved in mesothelioma tumor growth, suggests it may serve as a promising mesothelioma anti-cancer target.

mesothelioma, cancer stem cell, TG2, MET, HGF
**MS14.07: Tumor Treating Fields (TTFields) Reduce DNA Damage Repair Capacity in Malignant Pleural Mesothelioma, Leading to Effectiveness in Cellular and Animal Models**

Mumblat H1, Martinez-Conde A1, Braten O1, Tiku K1, Dor-On E1, Schneiderman R1, Porat Y1, Voloshin T1, Davidi S, Blatt R1, Shteingauz A1, Tempel-Brami C1, Zeevi E1, Lajterer C1, Shmuely Y1, Danilov S1, Haber A1, Giladi M1, Kinzel A2, Weinberg U1, Palti Y1

1Novocure, Haifa, Israel, 2Novocure, Munich, Germany

Parallel Mini-Symposia 14: Biology and Novel Targets, Virtual, May 9, 2021, 2:30 PM - 4:00 PM

**Objective:** Malignant pleural mesothelioma (MPM) is one of the most aggressive types of cancer, with a 5-year survival rate of only 10%. Tumor Treating Fields (TTFields) therapy is a noninvasive antimitotic modality that locoregionally delivers low intensity (1-3 V/cm), intermediate frequency (100-500 kHz), alternating electric fields to the tumor bed. In the STELLAR clinical trial in patients with MPM, TTFields treatment in combination with standard of care chemotherapy (pemetrexed and a platinum-based chemotherapy agent) has demonstrated elevations in median overall survival, without increases in systemic toxicity. Accordingly, this treatment received FDA-approval and a CE mark as first line therapy for unresectable, locally advanced or metastatic MPM. While efficacy of TTFields for MPM treatment is well-established, further evaluation of the underlying mechanism of action is warranted.

**Methods:** Human MPM cell lines (MSTO-211H and NCI-H2052) were treated with various frequencies of TTFields to determine the frequency that elicits maximal cytotoxicity. The effect of the optimal frequency of TTFields on γH2AX foci formation, a marker of DNA double strand breaks (DSB), was examined by fluorescent microscopy. Expression levels of DNA damage repair proteins was evaluated by immunoblotting. The cytotoxic effect of TTFields in combination with cisplatin or pemetrexed was also tested in the MPM cell cultures, and efficacy of combining TTFields with both chemotherapy agents was examined in vivo. C57BL/6 mice were inoculated subcutaneously with RN-5 cells and treated for 7 days with sham, TTFields or chemotherapy alone, or the two modalities together. Tumor volume was measured using MRI, and DNA damage within the tumor detected using immunohistochemistry.

**Results:** In both MPM cell lines, maximal cytotoxicity was demonstrated at a TTFields frequency of 150 kHz, accompanied by increases in DNA DSB formation and reduced expression of proteins from the DNA repair Fanconi anemia (FA) pathway: FANCA, FANCD2, FANCJ, and BRCA1. TTFields application in combination with cisplatin or pemetrexed significantly increased efficacy versus each treatment alone. An additive effect was elicited with TTFields-pemetrexed co-administration and a synergistic effect with TTFields-cisplatin co-treatment. In vivo, fold change in tumor volume was significantly decreased for TTFields concomitant with the chemotherapeutic agents (cisplatin + pemetrexed) versus control. The combination also produced increased expression of DNA damage proteins within the tumor bed compared to control animals or those treated with chemotherapy alone.

**Conclusions:** The efficacy of TTFields (150 kHz) in MPM was associated with increased DNA DSB and reduced FA pathway protein expression. This effect may account for the synergism elicited by TTFields and cisplatin co-treatment, as the latter is known to induce DNA damage that is repaired via the FA pathway. Overall, this research provides additional insights on the mechanism of action of TTFields for MPM, an approved modality for use against this malignancy.

TTFields, Mesothelioma, DNA damage

**MS15.05: US Asbestos Control Methods: Historical Review of Prevention and Policy to Eliminate Exposure and Eradicate Asbestos-Related Diseases and the Future**

Reinstein L1

1Asbestos Disease Awareness Org, Redondo Beach, United States

Parallel Mini-Symposia 15: Epidemiology and Asbestos Control, Virtual, May 9, 2021, 2:30 PM - 4:00 PM
Objectives: Nearly 40,000 American lives are lost to asbestos-related diseases each year. In efforts to raise awareness and prevent exposure, the Asbestos Disease Awareness Organization (ADAO) has worked with doctors, hospitals, and healthcare providers around the world to discuss prevention and awareness campaigns. However, asbestos remains the leading workplace carcinogen, claiming nearly 40,000 lives annually in the U.S. This presentation will detail the current prevention and policy methods as well as examine the role doctors and healthcare physicians have in asbestos control, prevention, and policy efforts.

Methods: Using government databases, peer-reviewed papers, and nearly seventeen years of organizational experience, the presentation will discuss which prevention methods are in place in the U.S. and will examine the impact physicians can have on prevention efforts and early detection of asbestos-caused diseases, especially in relation to the dangers of legacy asbestos. Between 1999 and 2015, the U.S. Centers for Disease Control and Prevention found 45,221 deaths of mesothelioma accounting for about one case diagnosed for every 100,000 people. The Global Asbestos Disaster study estimated that in 2016, 39,275 Americans died from asbestos-caused diseases including lung cancer (34,270), mesothelioma (3,161), ovarian cancer (787), larynx cancer (443) and chronic asbestosis (613). Meanwhile, in 1984, EPA released a structural report in which they stated, "It is estimated with 95 percent confidence that the number of buildings with asbestos containing sprayed- or troweled-on friable material is between 18,000 and 365,000 buildings, with a point estimate of 192,000 buildings." According to the Cleveland Clinic, "any building built before the 1970s could contain asbestos, especially old houses and offices from the first half of the last century." This leaves Americans at risk of asbestos exposure just by participating in daily activities, such as going to school, workplaces, or the store.

Results: Although asbestos mining imports and use has been banned in nearly 70 countries, it is still legal in the U.S. New research will confirm the U.S. imported more raw asbestos in 2020 than in 2019. Due to high asbestos consumption in the 1900s and without a ban, occupational, non-occupational, environmental, and consumer exposure pathways remain a health problem and provide a roadmap to asbestos’s hazardous past. Legacy asbestos found in homes, schools, and workplaces is a present and unseen danger around the nation. Since 2000, independent consumer and cosmetic product testing results continue to confirm that asbestos remains a public health threat to Americans. All of these issues have led to the introduction of the bicameral Alan Reinstein Ban Asbestos Now Act of 2019 with support from some 25 leading organizations including the AFL-CIO, the American Public Health Organization and others.

Conclusion: The United States would benefit from a stronger education system surrounding asbestos and the dangers of asbestos exposure. The national and international scientific community has greatly advanced ADAO’s education, advocacy, and community prevention and policy efforts.

MS15.06: Mesothelioma and Lung Cancer Incidence in a Prospective Cohort of Asbestos Exposed Workers With Asbestosis – Results of the MoMar Cohort


1Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany

Background: Asbestos can cause malignant mesothelioma as well as lung cancer. The risk of persons with benign asbestos-related diseases to develop these malignant neoplasms was estimated based on the data of the prospective MoMar cohort.

Methods: Between 2008 and 2018, nearly 2,800 workers formerly exposed to asbestos with benign asbestos-related diseases were recruited in Germany and examined annually. These diseases were recognized as occupational disease according to the German statutory regulations on occupational diseases. The number of new cases of mesothelioma and lung
cancer occurring during this period was related to the incidence in the male general population of Germany. Standardized incidence ratios (SIR) and corresponding 95% confidence intervals (95% CI) were calculated.

Results: In total 2,439 men were included in this analysis. During the observation period 40 mesotheliomas and 64 lung carcinomas occurred. The risk compared to the general population is statistically significantly increased for mesotheliomas (SIR=23.76; 95% CI 16.98 - 32.36) and for lung cancer (SIR=1.58; 95% CI 1.22 - 2.02). Non-smokers had a reduced risk of lung cancer (SIR=0.58; 95% CI 0.21 - 1.27), while ex-smokers (SIR=1.75; 95% CI 1.28 - 2.32) and smokers (SIR=3.28; 95% CI 1.64 - 5.86) showed a statistically significant increased risk. However, mesothelioma risk was not influenced by the smoking status.

Conclusion: Employees with recognized occupational asbestos diseases showed a greatly increased risk of developing mesotheliomas. Thus, even more than 25 years after the ban on the manufacture and use of asbestos in 1993, people formerly exposed to asbestos had an increased risk of developing asbestos-associated malignant neoplasms. Additionally, the risk of lung cancer was also increased by more than 50% for employees with benign asbestos-related diseases compared to the general population.

Lung cancer risk, mesothelioma risk, benign asbestos-related disease, occupational disease

**MS15.07: Gene X Environment Interaction in Cancer and in Mesothelioma: Opportunities for Prevention, Early Detection and Novel Therapies**

Carbone M1, Grzymski J2, Yang H1

1University of Hawaii Cancer Center, Honolulu, United States, 2Desert Research Institute, Reno, United States

Parallel Mini-Symposia 15: Epidemiology and Asbestos Control, Virtual, May 9, 2021, 2:30 PM - 4:00 PM

Objectives: The recent realization of the widespread impact of inherited pathogenic mutations in many cancers reflects the development of targeted NGS, WES, WGS and MLPA assays that allow the simultaneous analyses of multiple genes in germline and tumor DNAs. Several genes have been Recent data indicate that about 12% of human malignancies develop in carriers of germline mutations of various tumor suppressor genes or less frequently of activated oncogenes, a percentage that is likely to increase with further studies. Despite this growing recognition, free germline genetic testing for cancer patients is offered in only a few institutions, and is otherwise unavailable or expensive and, in the US, often not covered by health insurance. Presently, therefore, we are not identifying most germline mutations carriers: these individuals are unaware of their increased cancer risk and susceptibility to carcinogens. This creates an obvious although unseen health disparity: many lives that could be saved from cancer are not.

Mesothelioma is no exception. Following the initial discovery that susceptibility to mesothelioma was transmitted in a Mendelian fashion in certain families and the subsequent discovery that heterozygous germline BAP1 mutations cause mesothelioma— and other cancers— in affected carriers, an increasing number of mutations of various tumor suppressor genes has been linked to mesothelioma development. Experiments in mice suggest that in carriers of germline mutations of BAP1 and of other tumor suppressor genes, the risk of developing mesothelioma increases upon exposure to carcinogenic mineral fibers (gene X environment interaction, GxE).

The identification of carriers of germline mutations allows the implementation of precautions to decrease GxE and prevent, or at least delay, cancer in these individuals. Enrollment in early detection cancer screening programs and the parallel implementation of preventive measures, such as screening with ultrasound and magnetic resonance imaging (MRI), rather than computed tomography (CT) imaging, to diminish the risk of cancer caused by diagnostic/therapeutic interventional radiology together with surgical removal of pre-malignant lesion and early stage tumors, has been shown to significantly increase survival in patients affected by cancer syndromes. Thus, carriers, once identified, can begin these potentially life-saving procedures.

Methods and Results: To address this challenge, the Healthy Nevada Project (HNP), sponsored by the State of Nevada—a state in which the environment is rich in mineral fibers and other environmental carcinogens— and by Renown Health, is conducting free WES sequencing to an initial 125,000 Nevadians, to be extended to the entire State. Leveraging this unique resource with separate NIH
grant funding we are investigating in the HNP cohort for evidence of GxE interactions that may lead to preventive and early detection measures.

**Conclusion:** It is anticipated that similar initiatives will soon be initiated elsewhere and that genetic screening together with studies of GxE contributions to common adult cancers will help save lives, reduce health care costs and make a major dent in our battle with cancer.

**MS15.08: Trends in Mesothelioma Incidence Among Females in the United States: Are We Out of the Woods Yet?**

**Rajapakse P:**
1 Danbury Hospital, Yale School of Medicine, Connecticut, Danbury, United States

**Parallel Mini-Symposia 15: Epidemiology and Asbestos Control, Virtual, May 9, 2021, 2:30 PM - 4:00 PM**

**Objectives:** Malignant Mesothelioma (MM) is an insidious neoplasm arising from the mesothelial surfaces, most commonly from pleura. Approximately 70 percent of cases of pleural mesothelioma in the United States (US) are associated with documented asbestos exposure. The annual number of mesothelioma cases, which increased steeply from the 1970s through the mid-1990s, is expected to return to background levels by 2055 according to prediction models. Although the incidence of mesothelioma in males has shown a downward trend since 1991, the incidence in females has remained stable despite regulatory actions on the use of asbestos. The continuing occurrence of malignant mesothelioma deaths in persons aged <55 years suggests ongoing inhalation exposure to asbestos fibers and possibly other causative EMPs (Elongated Metal Particles). Our objective was to characterize the females who developed mesothelioma over the last 26 years to identify the differences in incidence by age, ethnic groups, location of residence and primary site.

**Methods:** Trends in the age-adjusted incidence of MM from 1991 to 2017 were analyzed in the Surveillance, Epidemiology, and End Results (SEER) 18 registry, a population-based cancer surveillance registry from 18 geographic regions representing the US population, using SEER*Stat version 8.3.8 (National Cancer Institute).

**Results:** Age-adjusted MM incidence in males in the United States decreased from 1.12 to 0.82 per 100,000, with an APC of -1.16% (95% CI, -1.48% to -0.83%) from 2000 to 2017. However, the incidence among females remained stable over the last 30 years. (from 0.43 to 0.42 per 100,000; APC -0.21% [95% CI, -0.63% – 0.22%; p-value >0.05]). 3986 female cases of MM were identified between 1991 and 2017, of which 89.4% were White, 6.1% were Black. 41% were above 75 years of age at diagnosis, 24.6% were between 65 to 74 years, 17.4% were between 55 to 64 years, 10.8% were between 45 to 54 years, and 6.2% were between 15 to 44 years. The most common primary site was pleura (75.2%) and the second most common site was peritoneum (13.7%) similar to the male population. The primary site was unknown in 0.8%. The percentage of deaths attributable to MM was significantly lower in females compared to males for unclear reasons. (chi-square statistic 4.12; p= 0.04, significant at p-value < 0.05). The highest number of deaths related to mesothelioma among females were reported from the White population in California who were above 75 years of age.

**Conclusion:** Despite regulatory actions and the steady decline in the use of asbestos, the annual incidence of MM in women in the US remains unchanged. Although this was initially presumed to be due to the increased life expectancy of the elderly population, we identified that there is a relatively young population who continues to be affected. This underscores the need for investigating indirect exposures to asbestos as well as to other EMPs (Elongated Mineral Particles). Ongoing community awareness, preventive efforts, and surveillance with a focus on the female population are recommended.

malignant mesothelioma, asbestos, elongated mineral particles, pleural mesothelioma, united states
**MS16.01: Fibulin-3 Is Not a Useful Diagnostic Biomarker in Malignant Pleural Mesothelioma: Final Results of the DIAPHRAGM Study**


1Glasgow Pleural Disease Unit, Queen Elizabeth University Hospital, NHS Greater Glasgow & Clyde, Glasgow, United Kingdom, 2Macmillan Cancer Support, Glasgow, United Kingdom, 3Cancer Research UK Glasgow Clinical Trials Unit, Glasgow, United Kingdom, 4Wythenshawe Hospital, University Hospital South Manchester, Manchester, United Kingdom, 5Forth Valley Royal Hospital, NHS Forth Valley, Perthshire, United Kingdom, 6Glasgow Royal Infirmary, NHS Greater Glasgow & Clyde, Glasgow, United Kingdom, 7Salford Royal NHS Foundation Trust, Salford, United Kingdom, 8Royal Alexandra Hospital, NHS Greater Glasgow & Clyde, Glasgow, United Kingdom, 9Royal Gwent Hospital, Newport, United Kingdom, 10University Hospital Galway, Galway, Republic of Ireland, 11St James’s Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, 12University College London, London, United Kingdom, 13Translational Pharmacology Laboratory, Institute of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom, 14Southmead Hospital, North Bristol NHS Trust, Bristol, United Kingdom, 15Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, United Kingdom, 16North West Anglia NHS Foundation Trust, Peterborough, United Kingdom, 17University Hospitals Plymouth NHS Trust, Plymouth, United Kingdom, 18Calderdale and Huddersfield NHS Foundation Trust, Huddersfield, United Kingdom, 19Inverclyde Royal Hospital, NHS Greater Glasgow & Clyde, Glasgow, United Kingdom, 20Sherwood Forest Hospitals, Sutton in Ashfield, United Kingdom, 21University Hospitals of Leicester NHS Trust, Leicester, United Kingdom, 22Northern General Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, 23Lancashire Teaching Hospitals NHS Foundation Trust, Lancashire, United Kingdom, 24Churchill Hospital, Oxford University Hospitals, Oxford, United Kingdom, 25Aberdeen Royal Infirmary, NHS Grampian, Aberdeen, United Kingdom

**Parallel Mini-Symposia 16: Biomarkers and Genetics II, Virtual, May 9, 2021, 2:30 PM - 4:00 PM**

**Objectives:** Fibulin-3 (F3) and SOMAscan® (SS) are blood biomarkers previously associated with high sensitivity and specificity for Malignant Pleural Mesothelioma (MPM) in retrospective studies. Subsequent results regarding F3 have been inconsistent. The primary objective of DIAPHRAGM was to definitively determine the diagnostic utility of F3 and SS in an adequately-powered, prospective, intention-to-diagnose study. We previously reported that SS was of no diagnostic value in patients presenting with suspected MPM, but can differentiate MPM from asbestos-exposed controls (AEC) (Internal Validation Sensitivity 91%, Specificity 75%, AUC 0.832). Herein, we report the diagnostic performance of F3.

**Methods:** Consecutive patients with suspected pleural malignancy (SPM) were recruited from 23 UK & Irish centres between December 2013 & December 2016. Biomarkers were drawn at first presentation, simulating clinical use, and before any pleural intervention. All cases had access to thoracoscopy and specialist MPM MDT review. Inclusion criteria were: SPM, fitness for sampling and consent. Patients with recent/in-situ chest drain were excluded. The minimum sample size was 600 (projecting at least 120 MPM). Plasma for F3 and serum for mesothelin was stored at -80°C within 2 hours. F3 was measured (4 technical replicates) using a commercially-available ELISA (BosterBio), since the USCN CloudClone ELISA used in previous studies exhibited unacceptable inter- and intra-assay variability. Mesothelin was measured using the Mesomark ELISA (Fujirebio). 109 AECs without pleural effusion were recruited and underwent identical sampling and analysis. This study was supported by Glasgow Experimental Cancer Medicine Centre funded by Cancer Research UK and Chief Scientist’s Office Scotland.

**Results:** 639 SPM patients and 114 AEC were recruited. 164/639 (25.7%) SPM were diagnosed with MPM. 140/164 MPM cases and 388/473 non-MPM cases (47.4% Secondary Pleural Malignancy, 52.6% Benign) were randomly selected for F3 and Mesothelin analysis using matched plasma and serum. Mean F3 was measured (4 technical replicates) using a commercially-available ELISA (BosterBio), since the USCN CloudClone ELISA used in previous studies exhibited unacceptable inter- and intra-assay variability. Mesothelin was measured using the Mesomark ELISA (Fujirebio). 109 AECs without pleural effusion were recruited and underwent identical sampling and analysis. This study was supported by Glasgow Experimental Cancer Medicine Centre funded by Cancer Research UK and Chief Scientist’s Office Scotland.

**Objectives:** Fibulin-3 (F3) and SOMAscan® (SS) are blood biomarkers previously associated with high sensitivity and specificity for Malignant Pleural Mesothelioma (MPM) in retrospective studies. Subsequent results regarding F3 have been inconsistent. The primary objective of DIAPHRAGM was to definitively determine the diagnostic utility of F3 and SS in an adequately-powered, prospective, intention-to-diagnose study. We previously reported that SS was of no diagnostic value in patients presenting with suspected MPM, but can differentiate MPM from asbestos-exposed controls (AEC) (Internal Validation Sensitivity 91%, Specificity 75%, AUC 0.832). Herein, we report the diagnostic performance of F3.

**Methods:** Consecutive patients with suspected pleural malignancy (SPM) were recruited from 23 UK & Irish centres between December 2013 & December 2016. Biomarkers were drawn at first presentation, simulating clinical use, and before any pleural intervention. All cases had access to thoracoscopy and specialist MPM MDT review. Inclusion criteria were: SPM, fitness for sampling and consent. Patients with recent/in-situ chest drain were excluded. The minimum sample size was 600 (projecting at least 120 MPM). Plasma for F3 and serum for mesothelin was stored at -80°C within 2 hours. F3 was measured (4 technical replicates) using a commercially-available ELISA (BosterBio), since the USCN CloudClone ELISA used in previous studies exhibited unacceptable inter- and intra-assay variability. Mesothelin was measured using the Mesomark ELISA (Fujirebio). 109 AECs without pleural effusion were recruited and underwent identical sampling and analysis. This study was supported by Glasgow Experimental Cancer Medicine Centre funded by Cancer Research UK and Chief Scientist’s Office Scotland.

**Results:** 639 SPM patients and 114 AEC were recruited. 164/639 (25.7%) SPM were diagnosed with MPM. 140/164 MPM cases and 388/473 non-MPM cases (47.4% Secondary Pleural Malignancy, 52.6% Benign) were randomly selected for F3 and Mesothelin analysis using matched plasma and serum. Mean F3 was measured (4 technical replicates) using a commercially-available ELISA (BosterBio), since the USCN CloudClone ELISA used in previous studies exhibited unacceptable inter- and intra-assay variability. Mesothelin was measured using the Mesomark ELISA (Fujirebio). 109 AECs without pleural effusion were recruited and underwent identical sampling and analysis. This study was supported by Glasgow Experimental Cancer Medicine Centre funded by Cancer Research UK and Chief Scientist’s Office Scotland.

**Results:** 639 SPM patients and 114 AEC were recruited. 164/639 (25.7%) SPM were diagnosed with MPM. 140/164 MPM cases and 388/473 non-MPM cases (47.4% Secondary Pleural Malignancy, 52.6% Benign) were randomly selected for F3 and Mesothelin analysis using matched plasma and serum. Mean F3 was measured (4 technical replicates) using a commercially-available ELISA (BosterBio), since the USCN CloudClone ELISA used in previous studies exhibited unacceptable inter- and intra-assay variability. Mesothelin was measured using the Mesomark ELISA (Fujirebio). 109 AECs without pleural effusion were recruited and underwent identical sampling and analysis. This study was supported by Glasgow Experimental Cancer Medicine Centre funded by Cancer Research UK and Chief Scientist’s Office Scotland.

**Results:** 639 SPM patients and 114 AEC were recruited. 164/639 (25.7%) SPM were diagnosed with MPM. 140/164 MPM cases and 388/473 non-MPM cases (47.4% Secondary Pleural Malignancy, 52.6% Benign) were randomly selected for F3 and Mesothelin analysis using matched plasma and serum. Mean F3 was measured (4 technical replicates) using a commercially-available ELISA (BosterBio), since the USCN CloudClone ELISA used in previous studies exhibited unacceptable inter- and intra-assay variability. Mesothelin was measured using the Mesomark ELISA (Fujirebio). 109 AECs without pleural effusion were recruited and underwent identical sampling and analysis. This study was supported by Glasgow Experimental Cancer Medicine Centre funded by Cancer Research UK and Chief Scientist’s Office Scotland.
1. This was inferior to the performance of mesothelin in differentiating MPM from non-MPM cases (Sensitivity 20%, Specificity 95%, AUC 0.71 (95% CI 0.65 – 0.77) and AEC (Sensitivity 36%, Specificity 95%, AUC 0.77 (95% CI 0.7 – 0.83).

**Conclusion:** In this adequately-powered, multi-centre, prospective, intention-to-diagnose study, the diagnostic performance of F3 was not sufficient to be of routine clinical value in patients presenting with suspected MPM. F3 was also not useful in differentiating MPM from AECs.

**Keywords:** Biomarkers, Mesothelioma, Fibulin-3, Mesothelin
MS16.02: A New Chick Embryo Model to Aid in the Development of Personalised Therapies for Malignant Pleural Mesothelioma

Barnett S1, Herrmann A1, Tripari M1, Poptani H1, Shackcloth M2, Sacco J1, Coulson J1

1University Of Liverpool, Liverpool, United Kingdom, 2Liverpool Heart and Chest Hospital, Liverpool, United Kingdom

Parallel Mini-Symposia 16: Biomarkers and Genetics II, Virtual, May 9, 2021, 2:30 PM - 4:00 PM

Objectives: Our overarching aim is to establish a non-mammalian in vivo model of malignant pleural mesothelioma (MPM) using fertilized hen’s eggs. The model is 3Rs-compliant and can be used to reduce/replace mouse models to evaluate new approaches for the personalised treatment of MPM. Our initial objectives were to (1) establish robust protocols for growing low-passage patient-derived MPM cell lines on the chorioallantoic membrane (CAM), (2) compare engraftment rates and tumour volume for MPM cell lines of different histological types and with different genetic profiles, and (3) assess the in vivo phenotype of resulting MPM tumours.

Methods: We dual-labelled (fluorescent/bioluminescent) two epithelioid MPM cell lines (sourced from MesobanK), both NF2 and P16 negative, but one BAP1 positive (MESO-12T) and one BAP1 negative (MESO-8T). These cells lines were implanted on the CAM at embryonic day 7 (E7). Bioluminescent imaging was used to monitor primary tumour volume and any metastases. At E14, experiments were terminated, and the tumours were excised to be characterised by histological staining for proliferation (Ki-67), vascularisation (α-smooth muscle actin) and BAP1, or for expression profiling. In addition, we are developing a patient-derived xenograft CAM model (CAM-PDX), using fresh MPM tumour fragments.

Results: In initial experiments, we observed tumour formation in all surviving embryos. Both BAP1 positive (MESO-12T) and negative (MESO-8T) cell lines were able to form tumours on the CAM, suggesting that the MPM cell lines engraft efficiently irrespective of BAP1 status. We are currently testing engraftment of an additional 10 MPM cell lines (MesobanK and ATCC) and will report on tumour volume, vascularisation and spread. We have successfully utilised bioluminescence to quantify primary tumour load and metastasis longitudinally for neuroblastoma and are optimising protocols for mesothelioma.

Conclusion: We have developed methodology for growing and analysing MPM cells in a chick embryo model. The MPM-CAM is a cost-effective, high-throughput model that is particularly well-suited to investigating cell growth, angiogenesis or invasion (local or metastasis). We have shown that MPM cell lines form tumours on the CAM irrespective of BAP1 status, highlighting that this in vivo model can also be used to test new therapies based on BAP1 stratification. We anticipate the CAM-PDX model will offer a complementary model that recapitulates tumour heterogeneity and may better reflect tumour microenvironment. Both of these biologically informative preclinical models offer the MPM community an alternative to murine models for the translation of in vitro studies and testing emerging therapeutic interventions.

Keywords: Chick embryo

Figure 1. Workflow for analysis of MPM tumours in chick embryo model.

iMig2021 VIRTUAL

PROGRAMME BOOK
**MS16.03: CDKN2A and MTAP Are Useful Biomarkers Detectable by Digital Droplet PCR to Identify Mesothelioma from Activated Mesothelial Phenotype**

Cheng Y\(^1\), Yuen M\(^1\), Zhuang L\(^1\), Linton A\(^1\,\,2\,\,3\), Clarke C\(^4\), McCaughan B\(^6\), Takahashi K\(^1\), Lee K\(^1\,\,3\,\,4\)

\(^1\)Asbestos Diseases Research Institute, Sydney, Australia, \(^2\)Concord Repatriation General Hospital, Sydney, Australia, \(^3\)School of Medicine, University of Sydney, NSW, Australia, Sydney, Australia, \(^4\)Anatomical Pathology department, Concord Repatriation General Hospital, Sydney, Australia, \(^5\)Sydney Cardiothoracic Surgeons, RPA Medical Centre, Sydney, NSW 2050, Australia, Sydney, Australia

Parallel Mini-Symposia 16: Biomarkers and Genetics II, Virtual, May 9, 2021, 2:30 PM - 4:00 PM

**Objectives:** Malignant Pleural Mesothelioma (MPM) is a deadly cancer with no effective treatment. Currently more than 15 biomarkers used in the clinic to differentially identify MPM, therefore, there is an emerging requirement to identify highly specific and sensitive detection method for the development of an improved, less invasive analysis of biomarker in of MPM. The co-deletion of CDKN2A and MTAP has been shown by researchers as a highly specific characteristic of MPM, which can potentially be utilized in the development of a less-invasive method to diagnose MPM. We have previously shown that deletion of CDKN2A is detectable by the droplet digital PCR (ddPCR) technique. This study aims to utilise ADRI’s extensive MPM collection to validate the detection of both CDKN2A and MTAP loss by ddPCR, which in turn could potentially be used in developing a less-invasive method of biomarker detection for MPM from cell-free tumour DNA.

**Methods:** This study included FFPE (120), fresh MPM tissue and plasma samples. Each of the three sample types were obtained from each individual MPM patient at the same time. Normal mesothelium was also collected and used as a control. Additionally, primary MPM cell lines were used as biomarker detection controls, as established from our previous publication. All samples were processed to isolate the DNA, which was subsequently used for ddPCR detection of CDKN2A and MTAP. FFPE samples were also analysed by FISH for CDKN2A and MTAP deletion, and MTAP immunohistochemistry (IHC) expression. Concordance of IHC and FISH with ddPCR were studied in all samples.

**Results:** Most cases showed a loss of both MTAP and CDKN2A when determined by FISH with similar results for MTAP IHC. Both MTAP and CDKN2A showed a high retention in normal mesothelium samples. We confirmed that CDKN2A and MTAP are often co-deleted in MPM samples, as determined by all three detection techniques. MTAP and CDKN2A were successfully analysed in all cases, with the exception of a few compromised FFPEs that were collected over 10 years ago. Our in-house designed ddPCR assays for CDKN2A and MTAP are useful in differentiated MPM from normal mesothelioma. These assays also allowed differentiation of MPM and normal donor blood (plasma). Most samples produced sufficient detectable copies for the reference gene and deleted CDKN2A or MTAP, once again a few FFPEs collected over 10 years ago did not provide sufficient reference copy numbers to differentiate the deletion of CDKN2A or MTAP was due to the quality of the samples.

**Conclusion:** Our results indicate that the co-deletion of CDKN2A and MTAP is a frequent occurrence in MPM. Detection by ddPCR shows high concordance with the current utilised FISH and IHC method. DdPCR can potentially be utilised for the future development of a less-invasive MPM-specific detection technique on MPM tumour DNA.

**Keywords:** Biomarker, mesothelioma, CDKN2A (p16), MTAP

**MS16.04: YAP1 Signaling Inhibitors Suppress the Mesothelioma Cancer Stem Cell Phenotype**

Eckert R\(^1\), Kandasamy S\(^2\), Adhikary G\(^1\), Rorke E\(^1\), Mickle M\(^1\), Eckert R\(^7\), Alexander H\(^2\), Friedberg J\(^1\)

\(^1\)University Of Maryland School Of Medicine, Baltimore, United States, \(^2\)Rutgers Robert Wood Johnson Medical School, New Brunswick, United States

Parallel Mini-Symposia 16: Biomarkers and Genetics II, Virtual, May 9, 2021, 2:30 PM - 4:00 PM

**Objectives:** Mesothelioma is an aggressive cancer that...
has a poor prognosis. Tumors develop in the mesothelial lining of the pleural and peritoneal cavities in response to asbestos exposure. Surgical debulking followed by chemotherapy is initially effective, but this treatment ultimately selects for resistant cells that form aggressive and therapy resistant recurrent tumors. YAP1/TAZ/TEAD signaling is an important survival cascade in mesothelioma. Our objective is to determine if different YAP1 inhibitors can curtail the mesothelioma cancer stem cell (MCS cell) malignant phenotype and reduce tumor formation.

**Methods:** Mesothelioma cancer stem cells (MCS cells) are a highly aggressive subpopulation present in tumors that are responsible for tumor maintenance and drug resistance. In the present manuscript, we use cell culture, tumor formation and biochemical methods to examine the impact of targeting YAP1/TAZ/TEAD on the MCS cell phenotype. YAP1, TAZ and TEADs are transcriptional mediators of the Hippo signaling cascade that activate gene expression to drive tumor formation.

**Results:** We show that two YAP1 inhibitors, verteporfin and CA3, attenuate the MCS cell phenotype. Verteporfin or CA3 treatment reduced YAP1/TEAD level/activity to suppress MCS cell spheroid formation, matrigel invasion, migration and tumor formation. These agents also increase MCS cell apoptosis. Moreover, forced expression of constitutively-active YAP1 antagonizes inhibitor action, suggesting that loss of YAP1/TAZ/TEAD signaling is required for response to verteporfin and CA3. These agents are active against mesothelioma cells derived from peritoneal (epithelioid) and patient-derived pleural (sarcomatoid) mesothelioma, suggesting that targeting YAP1/TEAD signaling may be a useful treatment strategy. Verteporfin and CA3 also suppress MCS cell xenograft tumor formation without evidence of adverse side effects. In each case, these agents inhibit YAP1/TAZ signaling and activate apoptosis in tumors.

**Conclusion:** We propose that verteporfin and CA3 suppress YAP1/TAZ/TEAD signaling leading to induction of apoptosis and that apoptosis mechanisms further degrade YAP1/TAZ/TEAD function ultimately leading to suppression of the aggressive MCS cell phenotype. These findings suggest that YAP1/TEAD targeting agents may be useful in the treatment of mesothelioma. Verteporfin has photosensitization side effects and cannot be used clinically, but CA3 is not a photosensitizing agent suggesting that CA3-related compounds may be candidate treatment agents.

**Keywords:** YAP Inhibitor, TAZ, TEAD, Mesothelioma Therapy, HIPPO Signaling, stemcells

**MS16.05:** PPARα and PPARγ Activation Is Associated With Pleural Mesothelioma Invasion, but Therapeutic Inhibition Is Ineffective in Preclinical Models

Orozco Morales L1,2, Rinaldi C1,2,5, de Jong E3, Lansley S4, Hope D1,2, Olasz B1, Casey T1,2, Lee G1, Balaguer P7, Piggott M1, Vrielink A1, Bosco A3, Gumer J4, Lake R1,2, Lesterhuis J1,2,3

1The University Of Western Australia, Nedlands, Australia, 2National Centre for Asbestos Related Diseases, Nedlands, Australia, 3Telethon Kids Institute, Nedlands, Australia, 4Murdoch University, Murdoch, Australia, 5Centre for Microscopy Characterisation and Analysis, Nedlands, Australia, 6Institute for Respiratory Health, Nedlands, Australia, 7Institut de recherche en cancérologie de Montpellier, Montpellier, France

**Parallel Mini-Symposia 16: Biomarkers and Genetics II, Virtual, May 9, 2021, 2:30 PM - 4:00 PM**

**Objectives:** Mesothelioma is a cancer that originates in the pleura of the lungs and invades the surrounding tissues. Its low survival rate is directly related to the aggressive local growth of the tumour cells. Most murine mesothelioma models involve non-invasive subcutaneous tumours, which do not represent the clinical condition of the disease. Preclinical models that better mimic the clinical phenotype are needed to further study what drives mesothelioma invasion and how to overcome the progression of this disease.

We compared mesothelioma cell lines that were injected either subcutaneously or intrapleurally and found that only the latter resulted in invasive and rapid growth. We aimed to identify regulators of mesothelioma invasion by comparing transcriptomic and metabolomic data from invasive and non-invasive murine mesothelioma tumours, in combination with in vitro invasion and proliferation assays using chemical probes and knock-out cell lines, and in vivo targeting experiments.
Methods: Syngeneic mesothelioma cell lines AB1 and AE17 were inoculated either subcutaneously (SC), or intrapleurally (IPL) in BALB/c and C57BL/6 mice, respectively. Pleural and subcutaneous tumours derived from these cell lines were compared using RNA sequencing and metabolomics analyses to identify possible biochemical targets for therapeutic intervention. In vitro binding assays and transcriptional reporter assays were used to measure binding and inhibition of the selected targets. Additionally, a second invasive model of mesothelioma was developed by inoculating engineered AB1-Luc cells intraperitoneally (IP) in BALB/c mice. These tumours were visualized using bioluminescent imaging. IP tumours were monitored over time following treatment with chemical probe GW6471 to functionally validate the identified targets.

Results: Pleural tumours showed markedly increased growth and invasion compared to subcutaneous tumours. RNA sequencing analysis showed 339 genes that were differentially expressed between the pleural and subcutaneous space in both the AB1 and the AE17 models. Of these 339 genes, 234 were upregulated in IPL (invasive) tumours, and 107 were upregulated in SC (non-invasive) tumours. Upstream regulator analysis and weighted gene correlation network analysis from the differentially expressed genes, as well as metabolomics analysis of the tumours, identified a metabolic program associated with invasive growth, with peroxisome proliferator-activated receptors alpha (PPARα) and gamma (PPARγ) as potential key regulators. Binding assays and transcriptional reporter assays demonstrated that chemical probe GW6471 is a potent dual PPARα/γ antagonist. In vitro invasion and proliferation assays showed that GW6471 had anti-mesothelioma efficacy. However, in mice, administration of GW6471 at doses providing sustained plasma concentrations above the IC50 values for both PPARs did not result in significant anti-mesothelioma efficacy.

Conclusion: We identified a gene co-expression network with transcription factors PPARα and PPARγ at its centre that was associated with invasive growth of pleural inoculated mesothelioma. However, we demonstrated that the in vitro antitumour effect of GW6471 is off-target and dual PPARα/γ antagonism alone is not a viable treatment modality for mesothelioma.

Keywords: Murine invasive model, mesothelioma, PPARα, PPARγ, invasion inhibition

MS16.06: Both Long-Fibre Carbon Nanotubes and Asbestos Induce Sporadic Pleural Mesothelioma Recapitulating Human Disease: A Role for Epigenetic Mechanisms in Disease Development

Zacarias Cabeza J1, Chernova T1, Galavotti S1, Cauchy P2, Sun X1, Craxton A1, Murphy F1, Powley I1, Bennett J3, Nakas A3, Greaves P4, Donaldson K5, Poland C5, Spriggs R1, Willis A1, MacFarlane M1

1MRC-Toxicology Unit/University of Cambridge, Leicester, United Kingdom, 2Max Planck Institute of Immunobiology and Epigenetics, Freiburg, Germany, 3UHL NHS Trust, Glenfield Hospital, Leicester, United Kingdom, 4Department of Cancer Studies/University of Leicester, Leicester, United Kingdom, 5MRC/University of Edinburgh/Centre for Inflammation Research, Edinburgh, United Kingdom

Parallel Mini-Symposia 16: Biomarkers and Genetics II, Virtual, May 9, 2021, 2:30 PM - 4:00 PM

Objectives: Malignant mesothelioma (MM) is an aggressive, fatal tumour of the pleura or peritoneum and is strongly associated with asbestos exposure. Malignant pleural mesothelioma (MPM) is the most common form with a latency of up to 40 years. Long amosite fibres (LFA) fail to clear through the lymph system and are retained in the pleura of exposed individuals. Manufactured carbon nanotubes (CNT) are similar to asbestos in terms of their high aspect-ratio and thus may pose an asbestos-like inhalation hazard (Chernova et al, Curr. Biol. 2017); however, the molecular mechanisms underlying CNT toxicity and carcinogenic potential have not been sufficiently explored.

Methods: By using a model of direct injection into the pleural cavity, we compared the molecular changes that occur at the mesothelium after pleural exposure to LFA or Long carbon nanotubes (CNT) over 20 months following injection. To examine the effects of pathogenic fibres on epigenetic signatures, the levels of DNA methylation and gene expression were analysed using array technology. As the development of mesothelioma is associated with gene alterations/deletion (Hmeljak et al, Cancer Discovery, 2018), we have tracked potential gene alterations at different exposure times throughout disease progression.
ABSTRACTS

by performing sequencing analysis after Capture array of specific genes.

Results: We show a common molecular signature in the molecular changes induced by long-CNT and LFA throughout disease progression leading to the development of sporadic malignant mesothelioma. Our DNA methylation, transcriptome and sequencing analysis show that DNA methylation, gene expression profiles, as well as the DNA sequence of specific genes are similarly altered in the presence of long CNT and LFA, compared to control mice at matched exposure times. Importantly, epigenetic changes induced by pathogenic fibres (long-CNT and Asbestos) occur at the pre-neoplastic stage of disease and thus may play a key role in progression of pleural inflammatory lesions to malignant mesothelioma.

Conclusion: Together, these data demonstrate that exposure to long CNT or Asbestos induce changes in the accessibility of the chromatin by DNA methylation, together with changes in the DNA sequence of several target genes during the development of mesothelioma. Together, these data demonstrate that exposure to long-CNT induces development of sporadic pleural mesothelioma, replicating the pathogenesis of human disease and highlights commonality in the hazard mechanism of long pathogenic fibres at the molecular level.

Keywords: Malignant Mesothelioma, Intrapleura Injection, Asbestos, Carbon Nanotubes, Epigenetics, Sequencing

Parallel Mini-Symposia 16: Biomarkers and Genetics II, Virtual, May 9, 2021, 2:30 PM - 4:00 PM

Objectives: Exhaled breath contains volatile organic compounds (VOCs) reflecting physiological and metabolic processes in the human body, making it suitable to assess one’s disease state. Breath analysis based upon VOCs has shown to be a promising tool for detecting malignant pleural mesothelioma (MPM) in a non-invasive way (Lamote et al, 2017, Eur Respir J). However, the biochemical origin of these VOCs remains unclear, limiting its clinical application. Therefore, to investigate which VOCs arise for the tumour cells themselves and to increase the breath model's performance, in vitro experiments where set up to analyse the VOCs in the headspace of different mesothelioma cell lines by gas chromatography-mass spectrometry (GC-MS).

Methods: Epithelioid (H2795), sarcomatoid (H2731) and biphasic (NKI04) mesothelioma cell lines were cultured in T175 culture flasks at 37°C and 5% CO2 atmosphere for 2-3 weeks. After the last passaging step, the cells were incubated for exactly 48 hours, after which 1600 mL of headspace air was sampled over a Tenax®GR adsorption column using an external pump (16min @100 mL/min) and was sent out for GC-MS analysis, as previously optimized. As controls, 1600 mL of headspace air was sampled from empty culture flasks (blank) and culture flasks only containing cell culture medium (DMEM F12 Glutamax, P/S, FCS), under the same conditions. Every experiment was performed in triplicate. After GC-MS analysis, the background VOC profile of a conditioned empty adsorption column was used to correct the obtained VOC data. Using unsupervised clustering algorithms and principle component analysis (PCA), the different conditions were discriminated.

Results: See Figure 1.

MS16.07: In Vitro Volatomics to Pinpoint Mesothelioma-specific Biomarkers

Janssens E1, Marcq E2, Mol Z3, Vandermeersch L3, Walgraeve C3, van Meerbeeck J1,4,5, Lamote K1,4

1Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Antwerp, Belgium, 2Center for Oncological Research, University of Antwerp, Antwerp, Belgium, 3Department of Sustainable Organic Chemistry and Technology, EnVOC Research Group, Ghent University, Ghent, Belgium, 4Department of Internal Medicine, Ghent University, Ghent, Belgium, 5Department of Pulmonology & Thoracic Oncology, Antwerp University Hospital, Edegem, Belgium
**Conclusion:** The different cell lines show different VOC profiles, even compared to empty flasks and culture medium. Although the controls induce a high number of VOCs, the cell cultures have shown to produce some VOCs that were able to discriminate between the different cell types. This in vitro approach has pinpointed mesothelioma cell-derived VOCs, which can now be compared to the VOCs detected in breath of MPM patients. These mesothelioma-specific VOCs hold furthermore promise to non-invasively subtype MPM, indicating a potential use as prognostic biomarkers and to improve the follow-up and management of asbestos-exposed individuals and mesothelioma patients.

**Keywords:** VOCs, headspace, in vitro, mesothelioma cell lines

**PL06.05: Biomarker Results from a Phase 2 Trial of DuRvalumab with First Line chEmotherApy in Mesothelioma (DREAM)**

**Cook A**<sup>1,2</sup>, Yip S<sup>5,6</sup>, Leslie C<sup>7</sup>, Brown C<sup>5,6</sup>, Stockler M<sup>5,6</sup>, Hill A<sup>2,8</sup>, McCoy M<sup>1,9</sup>, Lesterhuis W<sup>1,2,4</sup>, Nowak A<sup>1,2,3</sup>

<sup>1</sup>University Of Western Australia, Perth, Australia, <sup>2</sup>National Centre for Asbestos Related Disease, Perth, Australia, <sup>3</sup>Sir Charles Gairdner Hospital, Perth, Australia, <sup>4</sup>Telethon Kids Institute, Perth, Australia, <sup>5</sup>NHMRC Clinical Trials Centre, Sydney, Australia, <sup>6</sup>University of Sydney, Sydney, Australia, <sup>7</sup>PathWest, Perth, Australia, <sup>8</sup>Murdoch University, Perth, Australia, <sup>9</sup>St John of God Hospital Subiaco, Perth, Australia

**Plenary VI: Towards Tomorrow, Virtual, May 10, 2021, 12:30 AM - 2:00 AM**

**Objectives:** The single-arm, phase 2 DREAM study was designed to determine the activity, safety and tolerability of durvalumab, cisplatin and pemetrexed as first line...
therapy in Malignant Pleural Mesothelioma. The study met its primary endpoint, with 54% of 54 patients alive and progression free at 6 months, partial responses in 48% of participants, a median progression free survival of 6.9 months (95% CI 5.5-9.0) with a median overall survival of 18.4 months (95% CI 13.1-27). Here we report initial results from immunohistochemistry studies (PD-L1, CD8, CD56, STAT 1/3/6, and multiplex immunohistochemistry (IHC)) in samples collected from the DREAM trial.

Methods: Archival tumour samples from diagnostic biopsies were assessed for PD-L1 expression by immunohistochemistry using PD-L1 clone SP263 pre-dilute and visualised using the Ventana 3 step detection system OptiView. An analysis plan was developed a priori. PD-L1 expression was assessed as both Tumour Proportion Score (TPS) and Cell Proportion Score (CPS) using methods recommended in companion diagnostic testing in NSCLC. Positive staining was considered any perceptible linear cell membrane staining (partial or complete) in viable tumour cells. The percentage of positive staining tumour cells of the total assessable tumour cells was scored. Primary analysis was by positive (TPS ≥ 1%) versus negative (TPS < 1%) PD-L1 expression. For secondary analyses, expression levels were coded as <1%, 1% to <5%, 5% to <50%, and 50% or higher. The same analyses were applied to CPS. CD8, CD56 and STAT 1/3/6 protein expression were also assessed by IHC and scored subjectively by a pathologist. Multiplex IHC co-stained with DAPI, anti-cytokeratin, anti-CD8, Anti-PD-1, and Anti-PD-L1. Semi-automated image analysis software was used to determine cell density parameters and examine associations between multiplex imaging parameters and clinical outcomes.

Results: Tumour issue was available from 51 participants. PD-L1 expression was evident (TPS >1%) in 27 participants, and not evident (TPS ≤1%) in the remaining 24. There was no association between tumour expression of PD-L1 and PFS, with a median PFS of 6.3 months (95% CI 5.3-10.4 months) for patients with PD-L1 negative tumours, and 6.6 months (95% CI 5.5-9.0 months) for patients with PD-L1 positive tumours. Exploratory analyses showed no associations between PFS and either PD-L1 expression defined by other cut points for either TPS. Presence of CD56 positive natural killer (NK) cells in tumour was indicatively associated with survival; patients with CD56 positive tumours (n=12) having a median OS of 24.8 months compared to 13.7 months for patients with CD56 negative tumours (n=38), however this was not statistically significant. Results from STAT 1,3 and 6 IHC and multiplex IHC will also be presented.

Conclusion: There was no evidence of an association between PD-L1 expression using the SP263 clone and treatment outcomes in patients with malignant pleural mesothelioma receiving combination chemoimmunotherapy with cisplatin, pemetrexed and durvalumab. Association of CD56 positivity and survival requires further investigation in a larger cohort.

Keywords: immunotherapy chemoimmunotherapy durvalumab cisplatin pemetrexed PD-L1 histology biomarkers imaging

PL06.06: Decoding Intra-tumoral Histologic Heterogeneity in Malignant Pleural Mesothelioma using Single-Cell Transcriptomics

Severson D1, Freyaldenhoven S1, Wadowski B1, Hughes T2,3,4, Hung Y5, Jensen R6, Richards W7, Anderson J1, Wang V1, Dao M1, Shalek A2,3,4, De Rienzo A1, Bueno R1

1The Thoracic Surgery Oncology Laboratory and the International Mesothelioma Program (www.impmeso.org), Division of Thoracic Surgery and the Lung Center, Brigham and Women’s Hospital and Harvard Medical School, Boston, USA, 2Ragon Institute of MGH, Harvard, and MIT, Cambridge, USA, 3Department of Chemistry, Institute for Medical Engineering and Sciences (IMES) and Koch Institute for Integrative Cancer Research, MIT, Cambridge, USA, 4Department of Chemistry, Institute for Medical Engineering and Sciences (IMES) and Koch Institute for Integrative Cancer Research, MIT, Cambridge, USA, 5Department of Pathology, Massachusetts Hospital and Harvard Medical School, Boston, USA, 6Department of Biological Sciences, Virginia Tech, Blacksburg, USA

Plenary VI: Towards Tomorrow, Virtual, May 10, 2021, 12:30 AM - 2:00 AM

Objectives: Malignant pleural mesothelioma (MPM) comprises three histologic types: epithelioid, sarcomatoid, and a mixture termed biphasic. We and others have investigated whole transcriptome profiles of bulk MPM samples, providing insights into features of epithelial-mesenchymal transition in MPM tumor microenvironments.
(TME) and their relationship to histologic type. However, studies of heterogeneity across MPM tumors have not fully elucidated the role, if any, of TME in determining MPM histologic phenotype. The aim of this study was to characterize phenotypic subpopulations and genetic subclones in each MPM histologic type using single-cell RNA-sequencing (scRNA-seq).

Methods: One hundred and ten fresh tissue specimens were collected from 50 surgical resections. For 26 cases, only 1 sample was utilized for scRNA-seq. For 24 cases, multiple (2-6) samples from pre-defined anatomical regions were collected for a total of 84 specimens. Four normal pleura resections were included in the experiment as controls. Upon collection, samples were dissociated using the Miltenyi protocol (Miltenyi Biotec). scRNA was extracted according to the protocol using the Seq-Well S^3 platform and plexWell kit. Libraries were prepared using Illumina Nextera XT, sequenced with Illumina NextSeq or NovaSeq and mapped to the hg38 reference with STAR. Digital gene expression profiles were generated with Drop-seq tools. Quality control and downstream statistical analysis were performed using RStudio software (e.g., Seurat). Single-cell chromosomal number variants (CNVs) were called using inferCNV.

Results: Single-cell transcriptional profiles from 9 epithelioid MPM, 8 biphasic MPM, 3 sarcomatoid MPM, 1 MPM not-otherwise-specified, and 2 normal pleura cases were examined. Preliminary analyses of 67 samples identified 160,503 single cells, each expressing an average of 1,387 transcripts across 638 genes. Macrophages (28,887 cells), T-cells (22,690 cells), and B-cells (10,497 cells) were the most prominent immune cell types observed. Natural killer cells (4,037 cells), endotheliocytes (3,991 cells), alveolar epithelial cells (2,129 cells), neutrophils (1,583 cells), mast cells (1,391 cells), and dendrocytes (209 cells) were also identified. We also detected 46,175 cells expressing epithelial markers (e.g., MSLN, DSP), and 19,278 cells expressing mesenchymal markers (e.g., VIM, FN1). For the 54,354 cells isolated from epithelioid samples, 64.07% were found in epithelial-expressing and 2.49% in mesenchymal-expressing clusters. In sarcomatoid samples (57,113 cells), 3.44% of cells were found in epithelial-expressing and 23.19% of cells in mesenchymal-expressing clusters, and the plurality of cells were identified as macrophages (35.13%). In biphasic samples (41,635 cells), 22.36% and 9.79% of cells were in epithelial- and mesenchymal-expressing clusters, respectively. A comparable cell fraction from biphasic samples were identified as T-cells (22.16%), macrophages (12.26%), or B-cells (10.54%). We observed clonal populations within several tumors with MPM-associated CNVs, e.g. whole deletions of chromosomes 9, 13, and 22. These were confirmed with parallel whole exome analysis.

Conclusion: Our preliminary analyses of scRNA-seq data indicate that the observed ratios of cells with mesenchymal and epithelial markers are consistent with histologic diagnosis. High prevalences of immune infiltrates, especially macrophages, were observed in non-epithelioid specimens consistent with previous studies. The complete analysis of 110 samples (in progress) will provide new insight into the role of TME in histologic heterogeneity in MPM.

Keywords: single-cell RNA-seq, tumor heterogeneity, tumor microenvironment, and epithelial-mesenchymal-transition
P001: Combined Deletion of Bap1, Nf2 and Cdkn2ab Causes Rapid Onset of Malignant Mesothelioma in Mice


1Oncode Institute, The Netherlands Cancer Institute, Amsterdam, The Netherlands, 2The Netherlands Cancer Institute, Amsterdam, The Netherlands

Poster Session, Virtual, May 7, 2021

Objectives: Malignant mesothelioma (MM) is a highly aggressive tumor of serosal surfaces. The vast majority of cases of mesothelioma are linked to asbestos exposure. Loss of BAP1, NF2, and CDKN2AB tumor suppressor gene function is frequently observed in malignant mesothelioma. There is limited treatment option available with cisplatin and pemetrexed combination as the main frontline therapy with modest survival advantage. There is an urgent need of preclinical models that are fast, reproducible and that recapitulates human disease to test new treatment modalities. Our objective is to develop a mouse model of MM based upon the co-deletion of clinically relevant genes, such as Bap1, Nf2, and Cdkn2ab, for therapeutic purpose.

Methods: Mesotheliomas were induced by deleting Bap1, Nf2, and Cdkn2ab in the thoracic cavity of mice. The tumor and tumor microenvironment were characterized histologically. Furthermore, we performed gene expression, chromatin profiling and drug response profiling in tumor-derived primary cells. In addition, we employed this autochthonous model for testing current standard of care as a proof of concept treatment.

Results: The combined inactivation of Bap1, Nf2, and Cdkn2ab in thoracic cavity led to a highly aggressive mesothelioma with histopathological features and gene expression profile similar to human MM (figure 1). This includes the distinct inflammatory phenotype. Bap1 deletion alone does not cause MM but dramatically accelerates mesothelioma when combined with Nf2, Cdkn2a, Cdkn2b and p19Arf disruption (hereafter refer as BNC loss). The accelerated tumor development is invariably connected with EZH2 mediated redistribution of H2K27me3 towards promoter sites, and activation of the PI3K, MAPK pathway. The primary cells derived from mouse mesothelioma showed drug response profile similar to those observed in human MM. Treatment of BNC tumors with cisplatin and pemetrexed, the current frontline treatment modestly prolonged survival of the mice. This model shows rapid and synchronous onset as early as four weeks after the deletion of relevant alleles.

Conclusion: We have developed a mouse model that is fast and recapitulates human mesothelioma. The mouse model is an ideal model system to study the biology and pathogenesis of mesothelioma. Furthermore, the immunocompetence of this model, and the fast and synchronous tumor onset makes it very suitable to design and validate new treatment regimens for this deadly disease.

Keywords: Mesothelioma, BAP1, Polycomb, EZH2
P002: In-Silico Analysis Reveals Novel Potential Molecular Targets Associated With MPM Patient’s Survival

Bisceglia L, Morani F, Rosini G, Melaiu O, Landi S, Gemignani F

1University of Pisa, Pisa, Italy

Poster Session, Virtual, May 7, 2021

OBJECTIVES: Malignant pleural mesothelioma (MPM) is a rare tumor with an unfavorable prognosis originating from the mesothelial cells. Due to the aggressiveness of this cancer, a clear and successful drug strategy is lacking. Thus, the detection of novel targets for future therapies is a task not yet accomplished. Intending to identify genes relevant for the malignant transformation of the pleura, we started from scratch with a new search adding the novel information available on TCGA (The Cancer Genome Atlas) and GEO (Gene Expression Omnibus) websites, where 85 MPM specimens and 3 normal control tissues were analyzed for transcriptome, through next-generation sequencing. Differential expression analysis was performed and the over-expressed genes were selected to further investigation. To have a better and more complete understanding of the MPM gene expression we filtered our results with the available gene expression data of published manuscripts where the MPM specimens were compared to healthy pleural tissues or other cancer types. Furthermore, an integrated bioinformatics pipeline was developed and a total of 15 genes were selected for their function and their association with the MPM patient prognosis. Then, as experimental validation, we confirmed the expression of the 15 genes at the protein level in several malignant cell lines and a non-malignant one.

METHODS. All the in-silico analysis was conducted in R language, using specific packages, the most prominent are: DESeq2 for differential expression analysis, Survival for the Cox regression analysis and rbsurv for the likelihood-based survival model. A risk score system was employed and the Kaplan-Meyer curves were designed. The functional enrichment analysis was performed by the Toppfun tools. Besides, we analyzed the expression of the respective proteins in 6 MPM cell lines (Mero-14, Mero-41, Mero-95, ZL-55, REN, and MSTO) and one non-malignant cell line (MeT-5A) through western blotting.

RESULTS. In brief, 18048 genes were found differentially expressed in MPM patients. After literature filter, data processing and GO enrichment analysis three signatures were identified. Therefore, the bioinformatics pipeline conducted us to a final list of 15 genes over-expressed in MPM patients. These genes could be useful for the prognostic prediction of the MPM. We examined the over-expression of these genes at protein levels in the western blot analysis. Interestingly, CTHRC1 was over-expressed in all MPM cell lines (relative to MeT-5A), while SELE, SPARC, and UHRF1 in 5 out of 6.

CONCLUSION. We conducted an in-silico study, aimed at identifying a novel actionable target for MPM patients. Our results may provide novel molecules as possible drivers for sustaining the tumorigenic process. However, more studies are needed to be undertaken to better evaluate the cancer-driving role of the targets herewith identified.

mesothelioma, gene signature, in-silico, over-expressed gene, MPM

P003: Genes Differentially Expressed among Malignant Pleural Mesothelioma Histotypes


1Unit of Pathological Anatomy, University Hospital of Pisa, Pisa, Italy, 2Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy, 3Unit of Thoracic Surgery, University Hospital of Pisa, Pisa, Italy, 4Endoscopic Section of Pneumology, University Hospital of Pisa, Pisa, Italy

Poster Session, Virtual, May 7, 2021

OBJECTIVES: There are three main histotypes of Malignant Pleural Mesothelioma (MPM): epithelioid (E), biphasic (B) and sarcomatoid (S), with the latter one having the worst prognosis. Although crucial for prognosis stratification and treatment decisions, the classification of histological subtypes remains challenging, particularly with small pleural biopsies and for B-MPM, which shares both E- and S-MPM aspects.

We conducted an in-silico study, aimed at identifying a novel actionable target for MPM patients. Our results may provide novel molecules as possible drivers for sustaining the tumorigenic process. However, more studies are needed to be undertaken to better evaluate the cancer-driving role of the targets herewith identified.

mesothelioma, gene signature, in-silico, over-expressed gene, MPM
**Methods:** Gene expression analysis was performed using a NanoString custom panel including 117 genes already tested as a tool for differential diagnosis of MPM and benign pleural lesions. The analysis was performed on 17 B-MPM, 15 S-MPM and 31 E-MPM formalin fixed and paraffin embedded tissues.

An unsupervised cluster analysis of all genes and samples was performed using the Euclidean distance. Differentially expressed genes between MPM histotypes were determined by a moderated t-statistics (false discovery rate <0.05).

This study was supported by The Kazan McClain Partners’ Foundation.

**Results:** The unsupervised cluster (Figure 1) divided samples in three main groups enriched in S-MPM, E-MPM and B-MPM respectively. Significantly deregulated genes are reported in table 1.

**Conclusion:** Herein, we identified 63, 10 and 16 genes deregulated between E-MPM vs S-MPM, B-MPM vs S-MPM and B-MPM vs E-MPM respectively. These results deserve further validation to determine to which extent these genes could improve MPM subtyping.

**Keywords:** Mesothelioma, Histotypes, Biomarkers, Gene expression

---

**Table 1: differentially expressed genes among MPM histotypes.**

<table>
<thead>
<tr>
<th>E-MPM vs B-MPM (16 genes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITGAS, COL4A2, MMP1, CF8, MMP14, LAMCI, GLI1, MKI67, COL1A1, DNMT1, BUB1, NOTCH1, CENPF, FN1, BMP1, BIRC5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E-MPM vs S-MPM (63 genes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF8, CLDN15, MSLN, KRT5, CXADR, CDH1, ITGAS, NMU, ASS1, PTGIS, SERPINE1, COL4A2, LAMA3, EGFR, DSP, SFRP1, BU81, CAV1, MKI67, GLI2, CENPF, MMP9, PDGFRB, TUBB3B, FN1, ITGB4, NME2, MMP1, IFITM1, NDCB, PAK4, COL1A1, PLX1, CD274, RAD21, CCNB1, BIRC5, MMP7, HEG1, MMP14, ACSL1, SDHB, DNMT1, CDX1, PLK2, DNMT3A, PTGS2, CDSK, CCNO, ESR2, BMP1, UBE2T, VWF, LGALS3BP, ADAMTS8, EGR3, SMARC4, NOTCH1, TOP2A, CDH11, PPARA, EIF4G1, TTPP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B-MPM vs S-MPM (10 genes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAK4, NMU, CLDN15, GLI2, EGFR, SERPINE1, KRT5, NME2, CDH1, CXADR</td>
</tr>
</tbody>
</table>

E-MPM, epithelioid malignant pleural mesothelioma; B-MPM, biphasic malignant pleural mesothelioma, S-MPM, sarcomatoid malignant pleural mesothelioma.
P004: Hippo Imbalance Impacts on Chemotherapy Response of Malignant Pleural Mesothelioma Patients

Poma A1, Bruno R2, Pasquini G3, Ali G2, Proietti A2, Giordano M1, Macerola E1, Melfi F4, Lucchi M4, Chella A5, Fontanini G1

1Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy, 2Unit of Pathological Anatomy, University Hospital of Pisa, Pisa, Italy, 3Division of Medical Oncology, University Hospital of Pisa, Pisa, Italy, 4Unit of Thoracic Surgery, University Hospital of Pisa, Pisa, Italy, 5Unit of Pneumology, University Hospital of Pisa, Pisa, Italy

Poster Session, Virtual, May 7, 2021

Objectives: Hippo signalling is the most affected pathway in malignant pleural mesothelioma (MPM). This pathway is quite complex; however, it can be summarized in a kinase module, which acts as oncosuppressor, and a transcriptional one composed by oncogenes. The alterations that occur within this pathway are very heterogeneous. In the present study, we sought to understand how the expression levels of the Hippo core components affect the response of MPM patients to standard chemotherapy.

Methods: The expression levels of Hippo genes were assessed by a NanoString custom panel on 22 tumor tissues from epithelioid MPM patients treated with standard chemotherapy. Genes belonging to the very core of the kinase module (KM, n=13) and transcriptional module (TM, n=6) were averaged to build the KM and TM scores respectively. Patients were dichotomized by the median value of the KM/TM ratio. Survival curves were built with the Kaplan-Meier method and compared by Log-rank test. Hazard ratio (HR) was computed by Cox regression.

Results: In the high KM/TM ratio group there were 2 patients with stable disease (SD), 9 with partial response (PR) and 1 complete response. In the low KM/TM ratio group there were 3 progression disease, 2 SD, 4 PR and 1 not available. Patients with a high KM/TM ratio had a better progression-free survival (median 20 months, CI 95% 10 months to not reached, p=0.0095, Figure 1) than those with a low KM/TM ratio (median 9 months, CI 95% 6 to 13 months) and a HR of 0.26, CI 95% 0.09-0.77 (p=0.01).

Conclusion: By analysing the core genes of the kinase and transcriptional modules of the Hippo pathway, we found that their imbalance is associated with MPM patients response to chemotherapy. The pre-treatment identification of these patients could improve their management offering them other therapy options. Finally, it could be interesting to compare the KM/TM imbalance with the expression of YAP1 and phosphorylated YAP1 protein in order to obtain an easy-to-use biomarker.

Keywords: Mesothelioma, Chemotherapy, Hippo pathway, Biomarkers
P005: Analysis of Efficacy of Chemotherapy According to Histology in Malignant Pleural Mesothelioma (MPM) Patients


1Vall D’hebron University Hospital And Institute Of Oncology, BARCELONA, Spain

Poster Session, Virtual, May 7, 2021

Background: MPM is a highly aggressive pleural tumor associated with asbestos exposure and with limited survival despite systemic therapy. Histology is a prognostic factor, but its role as predictive factor is not well defined. The objective of this study is to characterize the impact of chemotherapy according to histology in patients (p) diagnosed with MPM at our institution

Methods: We review 189 MPM p diagnosed at Vall d’Hebron University Hospital between November 2002 and April 2020. Associations between clinical variables and outcome were assessed with Cox regression models and survival data were calculated by the Kaplan-Meier method.

Results: Patient’s characteristics: median age 68 years (y) (45-88 y), males: 70%, performance status (PS)1: 69%, asbestos exposure: 74%, epithelioid subtype: 76%. First line chemotherapy was offered to 85% of p (66% cisplatin-pemetrexed and 27% carboplatin-pemetrexed). Median survival (OS) in overall population was 21.3 m (95%CI17.2-24.3). Epithelioid histology, PS 0, and treatment with cisplatin vs carboplatin were associated with significant improvements in OS. Patients with epithelioid tumors had a median OS of 21.3 m versus 9.6 m no-epithelioid (HR 2.4 CI95% 1.6-3.4; p<0.001). Patients with PS 0,1 and 2 had a median OS 28.8 m, 18.8 m and 2.4 m respectively (HR 14.4 CI95%7.1-29; p<0.001). Patients treated in first line with cisplatin-pemetrexed had a median OS of 23.1 m versus 16.4 m for p treated with carboplatin-pemetrexed (HR0.44 CI95% 0.3-0.07, p<0.0005). For patients treated with chemotherapy in first line the progression free survival (PFS) was 4.4 m and the OS 23.1 m. In the analysis of efficacy of chemotherapy according to histology we found that patients with epithelioid tumors had better PFS and OS. Median progression PFS for p with epithelioid tumors treated with chemotherapy in first line was 4.8 m versus 3.6 months in no epithelioid tumors (HR 1.5 CI95% 1.0-2.3; p=0.03). OS for epithelioid patients treated with first line chemotherapy was 26.7 m versus 15.0 m in no epithelioid patients (HR2.25 CI95% 1.4-3.4; p<0.001).

Conclusions: In our series, patients with no epithelioid tumors presented worse prognosis. We confirmed histology is a prognostic factor with better OS for p with epithelioid tumors. Moreover, we demonstrated that histology is a predictive factor for efficacy of chemotherapy.

P006: Rare, Non-BAP1-Related Potential Tumor Predisposition Gene Variants in Families with Mesothelioma and Other Cancers Identified Using Whole Genome Sequencing

Cheung M, Kadariya Y, Ascoli V, Hall M, Ohar J, Testa J

1Fox Chase Cancer Center, Philadelphia, United States, 2Sapienza University of Rome, Rome, Italy, 3Wake Forest University School of Medicine, Winston-Salem, Unites States

Poster Session, Virtual, May 7, 2021

There is irrefutable evidence that inherited genetic alterations can contribute to malignant mesothelioma (MM) susceptibility. To date, one well-established predisposing factor, germline mutation of BAP1, has been identified. However, germline BAP1 mutations are not found in all instances of familial MM or in high-risk cancer families affected by various cancers, including MM.

Objectives: The goal of this study was to use whole genome sequencing (WGS) to determine the frequency and types of germline gene variants occurring in MM patients with a family history of cancer but without an inherited BAP1 mutation.

Methods: WGS was performed on blood DNA samples from 12 asbestos-exposed MM patients from high-risk
ABSTRACTS

P007: Dynamic Gene Expression Changes Underpin Checkpoint Blockade Response in Murine Models of Mesothelioma and Renal Cell Cancer

Chin W1,2,4, Casey T1,2, Lake R1,5, Nowak A1,2,4, Lassmann T3, Lesterhuis J1,3,5

1National Centre For Asbestos Related Diseases, Perth, Australia, 2University of Western Australia - Medical School, Perth, Australia, 3Telethon Kids Institute, Perth, Australia, 4Sir Charles Gairdner Hospital - Department of Medical Oncology, Perth, Australia, 5University of Western Australia - School of Biomedical Sciences, Perth, Australia

Poster Session, Virtual, May 7, 2021

Objectives: Despite the extensive use of antibodies that block immune checkpoints such as CTLA4 and PD-L1 in cancer, little is known about the dynamic biological events that underpin response to treatment. Using functional genomics, we employ both bulk RNAseq and single cell RNAseq data to identify differentially activated, time-dependent signalling pathways after treatment with immune checkpoint blockade.

Methods: Using AB1 mesothelioma and Renca kidney cancer mouse models, we sequenced tumours across 1 baseline and 3 subsequent time-points after combination checkpoint blockade treatment. From bulk RNAseq data, we constructed a time-dependent gene-regulatory network from responder and non-responder mice using the random forest-based algorithm GENIE3. Analysing the topology of this network, we isolated crucial genes showing differential, time-dependent activation in responders versus non responders.

Having identified this dynamic signal from bulk RNAseq data, we analysed single cell data from AB1 and Renca tumours harvested at treatment baseline. We used count imputation, pathway enrichment analysis, RNA velocity analysis and single cell network analysis to trace this signal to the relevant cell population in the tumour microenvironment.

Results: Using time-course bulk RNAseq data, we identify a crucial, fast-on, fast-off signalling pathway in common to checkpoint blockade responders in Renca and...
AB1 mesothelioma mouse models. We recapitulate this observation in AB1 single cell data, identifying pathway activation in tumour-associated monocytes. Using network analysis and RNA velocity analysis, we further show that pathway activation closely tracks the differentiation trajectory of these monocytes in the tumour microenvironment. Finally, we use canonical correlation analysis in combination with RNA velocity measurements to co-analyse monocytes from Renca and AB1 single cell samples, showing that that pathway activation across this monocyte trajectory is conserved in both of our murine models.

Conclusion: We identify a set of genes common to both Renca and AB1 which show dynamic expression changes specific to checkpoint blockade responders. These genes display distinct kinetics only in responders, suggesting their utility as predictive biomarkers to checkpoint blockade response. We trace the origin of this dynamic signal to monocytes in our murine cancer models.

Keywords: immune checkpoint blockade, network analysis, single cell sequencing

P008: Exploring Alternative Methods of Detecting ENOX2 – a Biomarker for Mesothelioma
Creaney J1,2, Dick I1, Rouse E1, Linthorne J1, Firth T1, Musk A1,2, Robinson B1,2
1National Centre For Asbestos Related Diseases, , Australia, 2Department of Respiratory Medicine, Sir Charles Gairdner Hospital, , Australia
Poster Session, Virtual, May 7, 2021

Objectives: ENOX2 (Ecto-Nicotinamide Adenine Dinucleotide Oxidase Disulfide-Thiol Exchanger 2) is a member of a family of cell surface proteins that oxidize reduced pyridine nucleotides [NAD(P)H] and are essential for cell enlargement and growth. We have shown that shed ENOX2 protein is detected in the serum of mesothelioma patients, in some cases ENOX2 was detected in the serum more than four years before the clinical development of symptoms [1]. This work was performed using two-dimensional (2D) gel electrophoresis and immunoblotting to detect mesothelioma-specific ENOX2 proteins. In order to undertake high throughput screening of samples a more robust assay is required.

(1) To characterise mesothelioma-specific ENOX2
(2) To evaluate different methods of measuring ENOX2

Methods: Clinical samples for study, including tumour tissue, non-malignant mesothelial cells, pleural effusions and serum were kindly donated by patients of Sir Charles Gairdner Hospital following written informed consent. Samples have been examined at the genetic and protein levels for ENOX2 expression. Whole exome sequencing data were analysed to identify mutations and copy number changes; whole RNA transcriptome data were analysed to perform gene-level differential expression analyses and identify potential novel splice isoforms. Protein levels were evaluated by Western blotting and ELISA using ENOX2-specific antibodies.

Results: ENOX2 was not significantly mutated in mesothelioma tumour at the DNA level. Novel RNA transcript splice forms were identified in a sub-set of mesothelioma tumours. Interestingly, tumour-associated splicing was also observed in non-malignant mesothelial cells. In mesothelioma tumour cells two protein bands of approximately 40 and 60 kDa are reactive with anti-ENOX2 antibodies.

Conclusion: ENOX2 variants are detected in the serum for several years before the clinical development of mesothelioma. Characterisation of ENOX2 expression in mesothelioma will be important for design of future mesothelioma-specific assays.

P009: National Centre for Asbestos Disease - Biobank
Creaney J1,2, Lee Y1,2, Nowak A1,2, Rouse E1, Firth T1, Robinson B1,2
1National Centre For Asbestos Related Diseases, , Australia, 2Sir Charles Gairdner Hospital, , Australia
Poster Session, Virtual, May 7, 2021

Objectives: Progress in mesothelioma research accelerated greatly with the availability of tumour and blood samples. The National Centre for Asbestos Related Disease (NCARD) has access to a large patient cohort
so it has expanded its biobank aim to collect and provide donated patient samples to facilitate research that will led to further improvement in the diagnosis and treatment of asbestos related disease as well as to expedite the development of early intervention strategies to reduce the burden of disease. The bank was established in 1994 with a focus on malignant mesothelioma and has collected samples from more than 1,000 mesothelioma patients, including blood, urine, tumour tissue and effusions. Importantly, the bank has also focussed on collecting samples from appropriate control populations, such as those at risk of mesothelioma, those with asbestos exposure but no mesothelioma and those where mesothelioma is part of the differential diagnosis pathway. In the process the bank has collected samples from individuals with a range of different benign and other malignant conditions.

To collect, store and distribute biospecimens and associated clinical data to support research aimed at improving diagnosis, treatment and prevention of mesothelioma.

**Methods:** All donors provide written, informed consent for collection of samples and clinical information to be collected for use in future non-specified research projects. Samples are processed using standardised protocols based on Australasian Biospecimen Network-Oncology guidelines. Requests to access samples for use in ethically approved research projects are reviewed by the NCARD Biobank Management Committee.

**Results:** The tissue bank has contributed resources towards >100 research projects and publications, including those of The Cancer Genome Atlas (TCGA) and the National Institute of Health, Early Detection Research Network as well as our own research funded by the National Health and Medical Research Council (NHMRC), SCGH Research Foundation and Cancer Council Western Australia. Genetic material has been contributed to international and national efforts to perform molecular characterisation of malignant mesothelioma. Serum samples from the biobank underpinned the development and commercialisation of the mesothelin biomarker, the only approved biomarker for mesothelioma. Pleural effusion analysis have led to review of their clinical management and utility. Pleural effusions provide a particularly useful resource not available in many cancers, in that the cells are tumour-associated and can be collected sequentially, allowing investigation of the dynamic changes in the tumour and immune system before, during and after therapy. Cell lines have been generated that support a range of projects exploring mesothelioma biology and drug sensitivity.

**Conclusion:** Such a biobank will provide key resources for translational research aimed at generating the knowledge to realize the goals of precision medicine and enable us to make better decisions and deploy more accurate therapies in mesothelioma, guided by more informative biomarkers. By facilitating access to samples and clinical data available through the NCARD biobank research into improving the outcomes for patients can be progressed. Samples from the NCARD biobank are available, upon application and approval, for the wider research community to facilitate diverse research outcomes.

**Keywords:** mesothelioma, biobank, NCARD, biomarkers, specimens

**P010: Relationship Between Asbestos Exposure and Epigenetic Age Acceleration in Malignant Pleural Mesothelioma**

Cugliari G1, Allione A1, Guarrera S2,3, Casalone E1, Gentilini D4, Grosso F5, Ferrante D6,7, Sculco M8, Aspesi A9, Libener R9, Migliore E10,11,12, Mirabelli D10,11,12, Magnani C6,7,10, Dianzani I8,10, Matullo G1,10,13

1Department Of Medical Sciences, University Of Turin, Turin, Italy, 2Italian Institute for Genomic Medicine, IIGM, Candiolo, Italy, 3Candiolo Cancer Institute, FPO - IRCCS, Candiolo, Italy, 4Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, 5Mesothelioma Unit, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, 6Unit of Medical Statistics, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy, 7Cancer Epidemiology Unit, CPO-Piemonte, Novara, Italy, 8Department of Health Sciences, University of Piemonte Orientale, Novara, Italy, 9Department of Integrated Activities Research and Innovation - Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, 10Cancer Epidemiology Unit, Department of Medical Sciences, University of Turin, Turin, Italy, 11Cancer Epidemiology Unit, CPO Piemonte,
**ABSTRACTS**

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Age is one of the strongest predictors of chronic disease and mortality. Aging denotes a multitude of processes at the cellular level, and biological responses to aging differ among people, having thus an important role when considering the relationship with other disease-related covariates.

**Methods:** DNA methylation (DNAm) profiles have been used to compute biological age. Using two previously established methylation-based “clocks” (proposed by S. Horvath), namely intrinsic epigenetic age acceleration (IEAA) and extrinsic epigenetic age acceleration (EEAA), we defined biological age acceleration for each of three hundred asbestos-exposed subjects. Asbestos exposure-related variation in age acceleration indices and 95% confidence intervals (CIs) were estimated using multiple linear regression models.

**Results:** EEAA showed that biological age acceleration was statistically significantly associated with increased asbestos exposure (Estimate = 0.704, 95% CI: 0.067, 1.475, P= 0.043).

**Conclusions:** Our results suggest the potential use of age acceleration measures from DNAm profiles in blood as a proxy of asbestos exposure assessment.

This will allow to develop non-invasive tests for asbestos-exposed subjects with the aim to best characterize and monitor early detection indicators in MPM.

**Acknowledgments:** This work was supported by Ministero dell’Istruzione, dell’Università e della Ricerca - MIUR project “Dipartimenti di Eccellenza 2018–2022”.

**P011: Relationship Between Stochastic Epigenetic Mutations and Asbestos Exposure in Malignant Pleural Mesothelioma**

**Cugliari G**1, Allione A1, Guarrera S2,3, Casalone E1, Gentilini D4, Grosso F5, Ferrante D6,7, Sculco M6, Aspesi A8, Libener R9, Migliore E10,11,12, Mirabelli D10,11,12, Magnani C6,7,10, Dianzani I8,10, Matullo G1,10,13

1Department Of Medical Sciences, University of Turin, Turin, Italy, 2Italian Institute for Genomic Medicine, IIGM, Candiolo, Italy, 3Candiolo Cancer Institute, FPO - IRCCS, Candiolo, Italy, 4Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, 5Mesothelioma Unit, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, 6Unit of Medical Statistics, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy, 7Cancer Epidemiology Unit, CPO-Piemonte, Novara, Italy, 8Department of Health Sciences, University of Piemonte Orientale, Novara, Italy, 9Department of Integrated Activities Research and Innovation - Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, 10Cancer Epidemiology Unit, Department of Medical Sciences, University of Turin, Turin, Italy, 11Cancer Epidemiology Unit, CPO Piemonte, Turin, Italy, 12Interdepartmental Center for Studies on Asbestos and Other Toxic Particulates “G. Scansetti”, University of Turin, Turin, Italy, 13Medical Genetics Unit, AOU Città della Salute e della Scienza, Turin, Italy

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Age is one of the strongest predictors of chronic disease and mortality. Aging denotes a multitude of processes at the cellular level, and biological responses to aging differ among people, having thus an important role when considering the relationship with other disease-related covariates.

**Methods:** DNA methylation (DNAm) profiles have been used to compute biological age. Using two previously established methylation-based “clocks” (proposed by S. Horvath), namely intrinsic epigenetic age acceleration (IEAA) and extrinsic epigenetic age acceleration (EEAA), we defined biological age acceleration for each of three hundred asbestos-exposed subjects. Asbestos exposure-related variation in age acceleration indices and 95% confidence intervals (CIs) were estimated using multiple linear regression models.
Results: EEAA showed that biological age acceleration was statistically significantly associated with increased asbestos exposure (Estimate = 0.704, 95% CI: 0.067, 1.475, P= 0.043).

Conclusions: Our results suggest the potential use of age acceleration measures from DNAm profiles in blood as a proxy of asbestos exposure assessment. This will allow to develop non-invasive tests for asbestos-exposed subjects with the aim to best characterize and monitor early detection indicators in MPM.

Acknowledgments: This work was supported by Ministero dell’Istruzione, dell’Università e della Ricerca - MIUR project “Dipartimenti di Eccellenza 2018–2022”.

Acknowledgments: This work was supported by the AIRC Foundation for Cancer Research in Italy [grant number IG21390] and partly by Ministero dell’Istruzione, dell’Università e della Ricerca - MIUR project “Dipartimenti di Eccellenza 2018–2022”.

Asbestos exposure; DNA methylation; age acceleration, Malignant Pleural Mesothelioma.

P012: The International Mesothelioma Program Database: Implementing a Relational Data Model to Support Collaborative Translational Research

Dao M1, Gustafson C1, De Rienzo A1, Bueno R1, Richards W1

1Brigham And Women’s Hospital, Boston, United States

Poster Session, Virtual, May 7, 2021

Objectives: The core mission of the International Mesothelioma Program (IMP) is multidisciplinary care, support, and research of patients with malignant pleural mesothelioma (MPM). Dedicated program staff have consistently and prospectively enrolled patients in clinical trials, collected and catalogued high-quality biospecimens, and recorded structured clinical and outcome data. Over two decades, these activities have established a large cohort of MPM tumors that have supported an expanding array of collaborative research in this rare cancer. Researchers have accumulated data regarding basic, translational, -omics, pre-clinical, and clinical trial studies that have potential to further annotate and add value to this resource. These datasets reside on different database management systems appropriate to their scale, ranging from REDCap for prospective clinical information to Microsoft SQL Server for clinical trial data, biospecimen data, and project management data; from LabArchives for laboratory research data to public/cloud repositories for large-scale omics data. The objective of this project is to link all of these separate datasets in a single relational model to facilitate collaborative translational research while maintaining patient privacy and the integrity of double-blind experimental design.

Methods: A custom, tiered-access user interface application is being developed in phases to provide de-identified connectivity among the various datasets. Each patient enrolled in a clinical study is assigned a unique internal participant identifier (ID) which provides a link among biospecimen/laboratory data and clinical PHI/PII. The first phase of development has involved constructing SQL queries joining existing SQL databases using the participant ID as a key. Subsequent phases will take advantage of the REDCap application programming interface (API) to control access to clinical parameters and the Freezerworks API to control access to biospecimen data. Authorization and credentials will be required to regulate access to different classes of data.

Results: Phase I development has resulted in a working application connecting data related to management of active and completed collaborative projects to biospecimens that have been shared, and datasets that have been returned. The overall object model and connectivity schema will be presented, along with projected phasing and timeline.

Conclusion: As the IMP biospecimen and data resource and collaborative projects continue to expand and mature, researchers at the IMP face an increasing challenge to integrate data from these disparate sources. The envisioned relational data model and user interface application will provide efficient connectivity, while requiring minimal change to existing resources, preserving patient privacy and conforming to regulatory requirements. Researchers will then be able to use one relational repository to extract information from previous and ongoing laboratory studies, clinical trials, and biospecimen allocations while respecting user roles and maintaining experimental integrity.
P013: Uptake and Efflux Transporter Polymorphisms Influence Cisplatin Treatment Outcome in Malignant Mesothelioma Patients

Dolžan V, Švarc M, Goričar K, Strbac D, Kovač V

1University Of Ljubljana, Faculty Of Medicine, Ljubljana, Slovenia, 2Institute of Oncology Ljubljana, Ljubljana, Slovenia

Poster Session, Virtual, May 7, 2021

Background: Platinum-based therapy is still widely used in treatment of malignant mesothelioma (MM), however the efficacy and toxicity of platinum agents vary greatly between patients. The aim of our study was to evaluate the influence of genetic polymorphisms in cisplatin uptake and efflux transporters on treatment outcome in MM patients.

Patients and methods: In total 194 MM patients treated with platinum-based therapy were genotyped for common SLC22A1 (rs628031), SLC47A1 (rs2289669), ABCB1 (rs1128503, rs2032582, rs1045642), ABCC2 (rs2804402, rs717620, rs2273697) and ABCG2 (rs2231137, rs2231142) polymorphisms. Logistic regression was used to test for possible associations with treatment response and survival (N = 194) as well as treatment related toxicities (N = 176).

Results: The investigated polymorphisms were associated with response rate neither in univariate, nor in multivariate analysis (adjusted for CRP and weight loss).

Progression free survival (PFS) was significantly longer in carriers of two polymorphic ABCB1 rs2032582 alleles (TT or TA) when compared to wild type homozygous patients (GG) in univariate analysis (OR=0.67 (0.47-0.96), P=0.031), however this association was lost in multivariate analysis (OR=0.73 (0.49-1.09), P=0.127; adjusted for histological type, smoking, weight loss and CRP). On the contrary, in carriers of polymorphic ABCG2 rs2231137 A allele, the protective effect on PFS was observed only after adjustment (OR=0.42 (0.18-0.99), P=0.047). Carriers of polymorphic SLC22A1 rs628031 A allele had significantly longer overall survival than non-carriers in univariate analysis (OR=0.66 (0.45-0.97), P=0.032), but not in multivariate analysis (OR=0.72 (0.49-1.07), P=0.103; adjusted for histological type, smoking, and CRP). Regarding treatment related toxicities, SLC47A1 rs2289669 polymorphism decreased the odds of treatment related thrombocytopenia (GA+GG vs. AA; univariate analysis: OR=0.42 (0.18-0.98), P=0.045; multivariate analysis: OR=0.38 (0.15-0.95), P=0.037, adjusted for pain at diagnosis and treatment regimen), as well as nephrotoxicity (GG vs. AA: univariate analysis: OR=0.34 (0.12-0.93), P=0.036). ABCB1 rs1045642 polymorphism decreased the odds of nausea/vomitus (CT+TT vs. CC; univariate analysis: OR=0.30 (0.10-0.85), P=0.024; multivariate analysis: OR=0.26 (0.08-0.82), P=0.022, adjusted for ECOG, pain at diagnosis and treatment regimen). The odds for alopecia were significantly increased in carriers of polymorphic ABCC2 rs2804402 genotype TT+TA genotypes increased the odds for alopecia when compared to GG (univariate analysis: OR=0.24 (0.09-0.65), P=0.005; multivariate analysis: OR=0.25 (0.08-0.81), P=0.022).

Conclusions: Our results suggest that polymorphisms of cisplatin uptake and efflux transporters influence survival and treatment-related toxicities in MM patients, therefore they should be further evaluated as potential genetic markers for the prediction of clinical outcome in MM patients.

cisplatin, genetic polymorphisms, malignant mesothelioma, transporters

P014: A Review of the Overlapping Genetic Mechanisms Between Ovarian Carcinomas and Malignant Mesothelioma

Ferretti A

1Brown University, United States

Poster Session, Virtual, May 7, 2021

Peritoneal malignant mesothelioma and ovarian carcinomas are histopathologically and symptomatically very similar diseases that do not have a reliable differential diagnosis. Immunohistochemical staining studies have
varying results with no general consensus on a singular method for diagnosis that will work everytime. By cross-referencing genetic alterations in studies of mesothelioma tumors and ovarian tumors, more cohesive insight into the genes altered in each disease could allow for more targeted research for developing diagnosis techniques, and even genetic-based therapeutic targets. This study focuses on the curated genes from the Comparative Toxicogenomics Database that are implicated in both asbestos exposure and malignant mesothelioma, as well as some genes highly correlated with genetic mesothelioma tumor profiles through GWAS studies. Each citation was thoroughly examined for ensuring that there was a significant result for each gene. These genes are used as keywords with each cancer to compile the best evidence that supports that the specified gene is an effective oncogene or therapeutic target. The results of this review emphasize the similarity of both diseases. The gene overlap shows how closely related the mechanisms of malignant mesothelioma and ovarian carcinomas are. Of the 52 genes and gene pathways evaluated, there were overlaps in 49 of them, particularly the genes TP53, KIT, COL3A1, BCL2, IL4, IL6, PARP1, and CDKN2A, and genes in the PI3K/AKT/mTOR pathway and hippo pathway. The genes affected in these tumor cells reflect homology in these tissues--both embryologically derived from the mesoderm--and the shared cascade of events promoting the cancer.

**P015: The Safety of Tumor Treating Fields (TTFields), An Anti-cancer Modality, When Delivered to the Torso of Healthy Rats**

Tiku K1, Blatt R1, Munster M1, Shteingauz A1, Cahal S1, Giladi M2, Weinberg U1, Palti Y1

1Novocure, Haifa, Israel

**Poster Session, Virtual, May 7, 2021**

**Objective:** Tumor Treating Fields (TTFields) therapy is a noninvasive, antimitotic modality that delivers alternating electric fields of low intensity (1-3 V/cm) and intermediate frequency (100-500 kHz) continuously to tumor bed. TTFields induce a cytotoxic effect in rapidly dividing cancer cells, with maximal outcome elicited at different optimal frequencies for various solid tumor cell-types. Based on clinical trial safety and efficacy results, TTFields therapy is approved for treatment of recurrent and newly diagnosed glioblastoma (at 200 kHz; alone or in combination with chemotherapy, respectively) in the USA, Europe, Japan, and China. The overall tolerable safety profile of TTFields in these patients is attributed to a lower rate of mitotic events in normal, quiescent brain cells. Specific safety evaluations are required for treating various solid tumor cancer types in the torso region that houses normal tissue with high cellular proliferation rates. This work describes the safety of delivering TTFields (as monotherapy) to the torso of healthy rats at 150 or 200 kHz, frequencies which were deemed optimally effective for treating a variety of torso residing tumor types.

**Methods:** TTFields at frequencies of 150 or 200 kHz were continuously applied to torsos of Sprague Dawley (SD) healthy, female rats using the Novo-TTF100L system. Throughout 2 weeks treatment duration, animals underwent daily clinical examinations. At treatment cessation, blood samples and major internal organs were analyzed for abnormal changes. Computer simulations were performed at in vivo experimental conditions to verify that the targeted internal regions of the torso were receiving TTFields at therapeutic intensities (≥1 V/cm).

**Results:** No treatment-related mortality was observed. The healthy animals treated with TTFields showed no significant differences versus control animals for the following parameters: activity level, food and water intake, stools, motor neurological status, respiration, weight loss, complete blood count, blood biochemistry, and histopathological findings. TTFields intensities of 1 to 2.5 V/cm RMS were calculated for the various torso internal organs.

**Conclusion:** Safety of TTFields at frequencies of 150 and 200 kHz and therapeutic intensities was demonstrated when applied to torsos of healthy rats, embodying normal tissues that exhibit high rates of cellular proliferation. This preclinical data was further underscored in phase II clinical trials, leading to additional ongoing studies in lung cancer (LUNAR Study, NCT02973789), pancreatic cancer (PANOVA-3 Study, NCT0377491), ovarian cancer (INNOVATE-3 Study, NCT03940196), gastric cancer (EF-31, NCT04281576), and hepatocellular carcinoma (HEPANOVA Study, NCT03606590). Studies in patients with malignant pleural mesothelioma have already allowed the approval of TTFields for treating this malignancy in the USA and Europe.

**TTFields, Safety, Torso**
**P016: Transcription Landscape Analysis of Malignant Pleural Mesothelioma: A Retrospective Study**

**Grosso F**, Inglesi A², Penpa S³, Callari M⁴, Lia M¹, De Angelis A¹, Roveta A³, Ugo F³, Mannarino L², Paracchini L², Hollander L², Rizzi N², De Simone I², Roca E², Marchini S², Barbieri P⁵, Libener R⁵, Mariani N⁶, Nozza P⁶, Maconi A³, D’Incalci M²

¹Mesothelioma Unit, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, EU, ²Department of Oncology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy, EU, ³IRFI, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, EU, ⁴Cancer Research UK Cambridge Institute University of Cambridge, Cambridge, United Kingdom, ⁵Department of Pathology, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, EU

**Poster Session, Virtual, May 7, 2021**

**Objectives:** In the present study we sequenced transcriptomes from 99 MPMs with known clinical data to identify transcriptional signatures that drive patients’ outcomes and response to therapy. From a histological point of view, MPM are broadly divided into three histological subtypes: epithelioid (eMPM), biphasic (bMPM) and sarcomatoid (sMPM). Patients with sMPM have particularly poor outcomes compared to patients with epithelioid histology. Most patients are diagnosed at advanced stages and the disease is largely unresponsive to conventional treatments e.g. chemotherapy or radiotherapy with an overall survival ranging from 8 to 36 months.

In this scenario, a detailed knowledge of the genetic alterations that drive and sustain MPM is critical for successful development of novel diagnostics, prognostics and personalized therapeutic strategies. Because MPM is rare, genomic studies have been limited and have typically involved a small number of samples.

**Methods:** A retrospective cohort of 99 Formalin-Fixed Paraffin-Embedded (FFPE) tumor samples from MPM patients was selected for the study. Cases included were diagnosed between 2005-2018 encompassing the three different histological subtypes. The study included: a) 74 patients with eMPM divided into 20 patients long survivor (>36 months) and 54 patients short survivor (<12 months) b) 25 patients with sMPM and bMPM. RNAseq experiments were performed on NextSeq-500 (Illumina) benchtop sequencer with a stranded library and with at least 60 millions reads per sample. RNAseq data were aligned using Hisat2, gene counts were assessed with Salmon and data were analyzed with DeSeq2.

**Results:** In line with data reported in literature we observed that eMPM, sMPM and bMPM have different transcriptional profiles, suggesting the different biology lagging behind the different histological subtypes. To define molecular subgroups of MPMs with prognostic significance, unsupervised consensus clustering of RNAseq–derived expression data from the analyzed samples has been performed. Algorithm has been used to characterize the different cell type populations, focusing on the immune infiltrating cells. To move one step forward in defining the biology of good and poor responder, genomic data has been integrated with histological analysis of tumor infiltrating cells. The transcriptional data has been integrated with the genomic mutational profile focusing on the genes that are more frequently mutated such as BAP1, NF2 and CDKN2A.

**Conclusion:** We expect that the results of this study could be potentially useful for patients’ stratification in relation to their transcriptional and molecular profiles. A better stratification of patients might be improved by integration with other available omic-data. The knowledge of the biological markers and their relationship with survival and tumor response in a retrospective clinical cohort of patients will significantly increase our understanding of the biology of this tumor and will pave the way to identification and/or development of novel drugs or combinatory approaches.

Keywords: transcriptomes, RNA-seq, genomic data

---

**P017: Overview of Legal Rulings, Literature and Trials Involving Use of Genomic Information in Litigation Involving Causation of Mesotheliomas and Other Phenotypes**

**Hartley K**

¹LSP Group - Law Science Policy, and ToxicoGenomica, Orland Park, United States

**Poster Session, Virtual, May 7, 2021**
**Objectives:** Provide a broad, objective summary of judicial and legislative decisions in the United States and other countries regarding gathering and/or using genomic data in legal proceedings in which a person is seeking money damages as compensation for developing a phenotype (e.g. mesothelioma, other cancers, birth defects) as an alleged or actual result of intake of a substance (e.g. asbestos, a drug, or a pesticide) that is claimed to have caused the phenotype. Some scholarly articles and decisions exist, and address topics such as limits, if any, on gathering and/or use of germline and/or somatic genomic data to shed light on whether hereditary germline variants or other genomic factors (e.g. transcription errors) were a complete or partial cause of a phenotype. Others address whether a physician or PhD can provide a proper differential etiology without genetic data if a genetic cause is plausible, and whether one or more genomic variants can induce a material level of susceptibility to a toxicant. The summary will be useful to persons with mesothelioma and their doctors who increasingly will find it helpful to understand litigation-related questions regarding personal and familial medical histories and/or genomic data.

**Methods:** Pertinent authorities will be gathered using key word searches of online, commercial legal databases. Authorities retrieved will be assessed by a lawyer with strong lay knowledge of genomics, and 35+ years of experience in litigation in the US and overseas. The reviewer is one of the authors of a chapter in Dr. Testa’s 2017 mesothelioma treatise: Chapter 17: Challenges Facing Mesothelioma Patients and their Families: Medical/Legal Intersections.

**Results:** Unlike prior presentations to iMig by other lawyers that focused on only one case, this will be a broad review. Review of databases is ongoing and will continue through April 2021. Some results already are known. With respect to mesothelioma in particular, the presentation will cover at least four recent US cases. Two are recent case in which whole genome sequencing was performed in cases involving younger persons (under 50) with mesothelioma, as well as personal and family histories that include multiple “red flags” suggesting hereditary disease. Two other cases are a fall 2020 ruling against genetic testing in a California mesothelioma case, and an Illinois case that produced a ruling allowing BAP1 testing, but not whole genome sequencing, after a two day evidentiary hearing in late December 2020 in which two PhDs testified. The latter two are ongoing and will be monitored for further decisions.

The review also will cover authorities in personal injury cases not involving asbestos or mesothelioma. They include 1) a series of rulings on “vaccinomics” issues in a series of cases involving vaccines, and 2) decisions on use of genomic information in personal injury lawsuits involving drugs, birth defects and/or pesticides. Results will include a table of recent, leading authorities, as well as analysis.

**Conclusion:** The presentation will assist physicians, PhDs and patients in understanding the increasing numbers of genomic medical/legal topics arising due to the ongoing revolution in molecular biology.

**P018: Exhaled Breath Analysis for Monitoring Therapeutic Response in Mesothelioma Patients Non-invasively**

**Janssens E**, **van Meerbeeck J**, **Lamote K**

1Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Antwerp, Belgium, 2Department of Internal Medicine, Ghent University, Ghent, Belgium, 3Department of Pulmonology & Thoracic Oncology, Antwerp University Hospital, Antwerpen, Belgium

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant pleural mesothelioma (MPM) is an aggressive cancer, with a five-year survival rate of <5%. Therapy is mostly palliative, including different combinations of chemotherapy, surgery, radiation and immunotherapy. Therapeutic response is monitored by CT scans using RECIST. Exhaled breath is easy to retrieve and contains volatile organic compounds (VOCs) that reflect metabolic processes in the human body, making it suitable to determine disease state. Recently, breath analysis has proven to be useful for MPM diagnosis (Lamote et al, 2017, Eur Respir J), allowing its exploration to monitor therapeutic response non-invasively. The aim of this study is to explore the possibility of monitoring therapeutic response by comparing VOCs in breath of treated and untreated MPM patients.

**Methods:** For this pilot study, breath samples were obtained from 15 untreated and 15 treated MPM patients.
VOCs in the breath samples were analyzed using a multicapillary column/ion mobility spectrometer (MCC/IMS).

**Results:** See Figure 1.

**Conclusion:** A significant difference in VOC profiles was observed in exhaled breath of treated vs untreated MPM patients (83% accuracy). Further research will determine if this difference is the result of tumor reduction, the presence of antitumoral agents or changes in inflammatory response. Comparisons with CT scans will also be made to see if there is a correlation with the clinical response rate.

**Keywords:** Mesothelioma, VOCs, Biomarkers, Response, Volatomics
**P019: Association Between microRNAs and Clinical, Inflammatory Factors in Patients with Malignant Pleural Mesothelioma Undergoing Multimodality Therapy**

Lauk O1, Orlowski V1, Neuer T1, Battilana B1, Schmitt-Opitz I1, Kirschner M1

1Department Of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland

Poster Session, Virtual, May 7, 2021

**Objectives:** Some clinical factors and molecular markers seem to have a prognostic impact in patients with malignant pleural mesothelioma (MPM), but aren’t fully clarified yet. Low platelet counts, hypoalbuminemia among others and microRNAs (miRNAs), small non-coding RNA molecules that regulate gene expression, may predict longer survival in patients with MPM, as previously published by Kirschner et al., 2014 (1). miRNAs may play a role in controlling inflammation and in the prevention of uncontrolled inflammation.

The aim of this analysis was to investigate possible correlations between tumor microRNA expression and clinical markers of inflammation, as well as to further evaluate their prognostic value prior to surgery.

**Methods:** Of 140 patients from our prospective database, who had undergone induction chemotherapy followed by extrapleural pneumonectomy (EPP) between 1999-2014, 67 patients had matching tissue samples available. The following blood parameters available after induction chemotherapy were analysed: white blood cells (wbc), platelets and C-reactive protein (CRP). Biopsies from diagnosis (before chemotherapy), as well as intraoperative tissue samples were collected for all patients and analyzed for 6 miRNAs (miR-21-5p, -23-3p, -30e-5p, 221-3p, -222-3p).

WBC, platelets, CRP and the 6 miRNAs were correlated using Kendall’s tau_b correlation test for continuous variables. Overall survival (OS) was calculated with Kaplan Meier analysis and tested with long rank test.

**Results:** The majority of patients were male (n=59) and of epithelioid histotype (n=55).

The analysis revealed weak, but significant correlations between preoperative platelets and miR-221 (r=0.19, p=0.03), as well as preoperative CRP and miR-21 (r=0.18, p=0.03), -23a (r=0.24, p=0.01), -221 (r=0.28, p=0.001) and -222 (r=0.17, p=0.05) (intraoperative tissue samples) and miR-21 (r=0.17, p=0.04) and -23a (r=0.17, p=0.04) (tissue samples from diagnosis). The following molecular markers showed a positive influence on OS, if expressed lower: miR-23a (32 months vs 18 months; p=0.004), miR-221 (32 months vs 19 months; p=0.01) at time of diagnosis and miR-23a at time of surgery (29 months vs 19 months; p=0.04).

**Conclusion:** We identified several statistically significant correlations between preoperative inflammatory and blood parameters (CRP and platelets) and intratumoral microRNA expression at EPP, suggesting a link between inflammation and microRNA expression. In addition, in line with previous data, the analysis revealed a statistically significant improvement of OS for 2 miRNAs available at time of diagnosis. More in-depth studies of the observed correlations are ongoing, also investigating the potential of combined inflammatory/microRNA markers as prognosticators, which could be used for selection of patients undergoing multimodality therapy.

**Keywords:** microRNAs, prognostic biomarkers, inflammation, survival

**P020: The Role of Secretary Leukocyte Peptidase Inhibiter (SLPI) in Pleural Effusion for the Differential Diagnosis of Benign Asbestos Pleurisy from Pleural Mesothelioma and Other Effusions**

Kishimoto T1, Fujimoto N1, Kojima Y1

1Research And Training Center For Asbestos-related Diseases, Okayama, Japan

Poster Session, Virtual, May 7, 2021

**Objectives:** For the diagnosis of benign asbestos pleurisy (BAP), various markers in pleural effusion were
investigated for the utility of differential diagnosis from BAP to malignant pleural mesothelioma (MPM) or lung cancer and other pleural effusions.

**Methods:** For 6 years from January 2013 to 2019, pleural effusion obtained in Okayama Rosai Hospital were used. Fifty one patients are BAP, 37 patients are MPM whose histology are 33 epithelioid and 4 sarcomatoid, 77 patients are lung cancer. Other pleural effusion contains 27 heart failure, 47 bacterial pleuritis including tuberculosis.

Investigated markers are followings; 1. SLPI, 2. Galectin-3, 3. CCL2=MCP1 (Monocyte chemoattractant Protein 1) 4. CYFRA21-1, 5. SMRP (soluble mesothelin related peptides)

6. Hyaluronic acid (HA) The diagnosis of BAP, cytological examination should be Class I or II. Furthermore, no irregular pleural thickening including mediastinal pleura or tumorous shadows existed by chest CT.

**Results:**

1. SLPI
Median of SLPI in pleural effusion for BAP was 53.22ng/mL ranged 21.2 from 122.13 ng/mL. Median for MPM was 118.62g/mL, lung cancer 85.04ng/mL and other pleural effusion was 77.45ng/mL. SLPI of BAP was significantly (p<0.0001) lower than other effusions. ROC analysis between BAP and MPM, AUC is 0.902 and cut off value was 82.9ng/mL with sensitivity 82.4% and specificity 86.5%.

2. Galectin-3
Median of Galectin 3 for BAP was 8.4ng/mL. Median for MPM (p<0.004) was 32.4ng/mL, Lung cancer (p<0.001) 15.5ng/mL and other pleural effusion (p<0.002) was 13.7ng/mL. Galectin 3 of BAP was significantly lower than other effusions.

3. CCL2
Median of CCL2 for BAP was 4,438pg/mL. Median for MPM (p<0.02) was 2149pg/mL, lung cancer (p<0.0001) 1,369pg/mL and other pleural effusion (p<0.0001) 1,070pg/mL. CCL2 of BAP was significantly higher than other effusions.

4. CYFRA21-1
Median of CYFRA for BAP was 15.6ng/mL. Median of MPM was 75.9ng/mL, Lung cancer 37.8ng/mL were significantly (p<0.0001) higher than BAP. Other pleural effusion was 9.2ng/mL. CYFRA of BAP was significantly (p<0.03) higher than other pleural effusion.

5. SMRP
Median of SMRP for BAP was 6.9nmol/L. Median for MPM was 16.7nmol/L and significantly (p<0.0001) higher than BAP. Lung cancer was 6.2nmol/L and the difference between these 2 diseases were no significance. Median of other pleural effusion was 4.9nmol/L and significantly lower than BAP (p<0.001) ROC analysis between BAP and MPM, AUC is 0.746.

6. HA
Median of hyaluronic acid for BAP was 30,000ng/mL, MPM was 89,200ng/mL, Lung cancer 23,400ng/mL and other pleural effusion was 17,750ng/mL. HA of BAP was significantly (p<0.0001) lower than MPM, but was significantly higher than lung cancer (p<0.004) and other pleural effusion (p<0.0001). ROC analysis between BAP and MPM, AUC is 0.902

**Conclusion:** SLPI is the most important marker for the differentiation BAP from MPM and other pleural effusion, because the value is significantly (p<0.0001) lower than other diseases, and ROC between BAP and MPM, AUC is 0.902 similar to HA.

Keywords: BAP  MPM  SLPI SMRP Hyaluronic acid

**P021:** External Validation of a Breath Test for the Diagnosis of Malignant Pleural Mesothelioma: Results of an Interim Analysis

**Lamote K**2, Janssens E1, Surmont V2,3, Nackaerts K4, van Meerbeeck J1,2,5

1Laboratory Experimental Medicine and Pediatrics, Antwerp University, Wilrijk, Belgium, 2Internal Medicine, Ghent University, Ghent, Belgium, 3Long Oncological Network Gent (LONG), Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium, 4Respiratory Medicine, University Hospital Gasthuisberg, Leuven, Belgium, 5Pulmonology & Thoracic Oncology, Antwerp University Hospital, Edegem, Belgium

Poster Session, Virtual, May 7, 2021
Objectives: Malignant pleural mesothelioma (MPM) is an aggressive thoracic cancer with a very poor prognosis, partly due to diagnosis at advanced stage. This stresses the need for new biomarkers that could aid in the early diagnosis of MPM. Recently, non-invasive breath biomarkers, called volatile organic compounds (VOCs), arose as potential biomarkers for this purpose. A series of consecutive studies, called ‘MesoBreath’, were previously performed by our research group in which a breath test for the detection of MPM was developed and internally validated. This showed a promising possibility to use breathomics as exclusive screening tool. The next step is to externally validate this test and subsequently assess the clinical validity and utility of the breath model. Therefore, a prospective multicentre study including an independent, international patient group is currently running. In order to look for potential confounders and to optimize the test, an interim analysis was done.

Methods: Breath and background samples were taken from 50 occupational asbestos-exposed individuals (AEx) and 4 treatment-naive mesothelioma patients. VOCs in these samples were analysed by multicapillary column/ion mobility spectrometry as previously described and the obtained raw data was further processed using VisualNow® software. The exhaled VOC profiles were corrected for background contamination. The previously developed breath model was then used to predict the condition of the participants based on their exhaled VOC profile (Lamote et al. Eur Respir J, 2017).

Results: Patients and controls were comparable between the training and validation set (Figure 1A). Considering the use as an exclusive screening tool, the cut-off was chosen to maximize sensitivity and negative predictive value (Figure 1B). This ensures that no MPM patients will be missed and MPM can be ruled out with certainty in the large number of screenees where the test is negative.

Conclusion: These preliminary results indicate that our breath test with maximal sensitivity and NPV could be useful for future screening of persons at-risk for MPM and ruling out disease. However, at this stage, a lot of AEx persons tested false positive. Nevertheless, implementing this test as a first screening step could yet potentially exclude 18% of AEx to be subjected to CT-scans for diagnosis. For the further course of this validation study, we aim to (1) increase the number of included individuals, (2) optimize our breath model to reduce the false positive rate and (3) perform in vitro experiments to identify more mesothelioma-specific VOCs and increase the specificity.
P022: Headspace Analysis of Volatile Organic Compounds from Malignant Mesothelioma Cell Lines

Little L¹, Carolan V¹, Allen L¹, Cole L¹, Haywood-Small S¹
¹Sheffield Hallam University, Sheffield, United Kingdom

Poster Session, Virtual, May 7, 2021

Headspace Analysis of Volatile Organic Compounds from Malignant Mesothelioma Cell Lines.

Objectives: Malignant pleural mesothelioma (MPM) is associated with a delayed diagnosis, an extremely poor 5-year survival rate and limited treatment options. Volatile organic compounds (VOCs) identified in exhaled breath have been used to discriminate MPM patients from other clinical groups, potentially providing a novel method of early diagnosis (Lamote et al., 2014). This research used solid-phase microextraction (SPME) and gas chromatography-mass spectrometry (GC-MS) to identify VOCs in the headspace of the biphasic MPM cell line MSTO-211H, the epithelioid MPM cell line NCI-H28 and the non-malignant mesothelial cell line MET-5A (Little et al., 2020). Treatments with hydrogen peroxide (H2O2) were performed to identify VOCs associated with oxidative stress in MET-5A cells.

Methods: A SPME fibre was exposed to the headspace gas of MSTO-211H, NCI-H28 and MET-5A cell cultures to extract VOCs. After extraction the SPME fibre assembly was injected into a GC-MS for VOC analysis. For oxidative stress experiments MET-5A cells were treated with H2O2 and headspace VOCs analysed.

Figure 1: Multivariate statistical analysis was applied to MSTO-211H, NCI-H28 and MET-5A GC-MS data. PCA showed that the VOCs produced by the three cell lines were beginning to separate. OPLS analysis confirmed that the VOC profiles produced by MSTO-211H, NCI-H28 and MET-5A were able to differentiate the three groups.
**Results:** Figure 1 and Table 1 show headspace analysis results from MSTO-211H, NCI-H28 and MET-5A cells. Initial results from oxidative stress experiments also showed that 2-hydroxy-propamide, 2-pentanone, 1,2,4-tricholorobenzene and naphthalene were increased in H2O2 treated MET-5A cells, whereas tetradecane was decreased.

**Conclusion:** VOC analysis has the potential to identify MPM at a much earlier stage than current methods, highlighting it as a valuable methodology in the search for novel diagnostics. The in vitro breath analysis model appears to discriminate between biphasic and epithelioid MPM cells in addition to non-malignant controls. This research identified specific increases in VOCs in MPM cells compared to non-malignant controls, indicating potential diagnostic targets. This model can also be used to study the effects of biological processes on VOC output, such as oxidative stress caused by H2O2.

Malignant pleural mesothelioma, volatile organic compounds, breath analysis, biomarkers, diagnosis
**P023: Novel MicroRNAs as Potential Biomarkers in Malignant Mesothelioma Patients from Hand-spinning Asbestos Exposure Area in Southeastern China**

Lou J¹, Zhu L¹, Ying S¹, Jiang Z¹, Zhang X¹

¹Zhejiang Academy Of Medical Sciences, Hangzhou, China

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant mesothelioma (MM) is an occupational aggressive malignant tumor of mesothelial origin that develops mainly in the parietal pleura or peritoneum, which is strongly associated with asbestos exposure. Our aim is to study the differential expression of miRNAs in MM patients and find the potential biological markers for diagnosis and differential diagnosis.

**Methods:** We sequenced miRNAs in formalin-fixed paraffin-embedded (FFPE) tumor tissue of MM compared with its adjacent normal tissue, and the expression of four differential miRNAs were selected for miRNAs validation using in Situ Hybridization verification method. Moreover, the expression difference of these four miRNAs in the plasma were also compared between lung cancer (LC) patients, patients with pleural plaques (PP), asbestos exposure (AE) subjects and healthy controls by qPCR.

**Results:** We found that a total number of 31 miRNAs were differentially expressed in tumor tissue of mesothelioma patients as compared to the tissue adjacent to carcinoma, with 18 miRNAs up-regulated and 13 miRNAs down-regulated. The elevated expression of miR-19b, miR-26a, miR-26b, and miR-29a in FFPE tumor tissue were furtherly validated in both the cytoplasm and the nucleus using FISH hybridization assay. Furthermore, the plasma expression levels of miR-19b and miR-29a in mesothelioma group were significantly higher than those in any other four groups, and similar expression difference were found in miR-26a and miR-26b between mesothelioma group and any other group except of lung cancer group. Diagnostic value analysis indicated high sensitivity and specificity of these four miRNAs in distinguishing MM patients from PP patients, AE subjects, and healthy controls.

**Conclusion:** Our study suggests miR-19b, -26a, -26b and 29a are potential serum biomarkers for early diagnosis of MM.

**Keywords:** microRNA, tissue microarray, malignant mesothelioma, biomarker, asbestos exposure

---

**P024: DNA Methylation Biomarker as Predictor of Survival in Patients with Malignant Pleural Mesothelioma**

Cugliari G¹,², Casalone E¹,², Guarrera S¹,², Allione A¹,², Viberti C¹,², Grosso F³, Betti M³, Ferrante D⁴,⁵, Sculco M⁶, Aspesi A⁶, La Vecchia M⁶, Casadio C⁷, Libener R⁸, Piccolini E⁹, Mencoboni M¹⁰, Mirabelli D¹¹,¹²,¹³, Magnani C⁴,⁵,¹³, Dianzani I¹⁰,¹¹, Matullo G¹¹,¹²,¹³,¹⁴

¹Department Of Medical Sciences, University Of Turin, Turin, Italy, ²Italian Institute for Genomic Medicine, Turin, Italy, ³Division of Medical Oncology, SS. Antonio e Biagio General Hospital, Alessandria, Italy, ⁴Medical Statistics and Cancer Epidemiology Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy, ⁵Cancer Epidemiology Unit, CPO-Piemonte, Novara, Italy, ⁶Department of Health Sciences, University of Piemonte Orientale, Novara, Italy, ⁷Thoracic Surgery Unit, AOU Maggiore Della Carità, Novara, Italy, ⁸Pathology Unit, SS. Antonio e Biagio General Hospital, Alessandria, Italy, ⁹Pneumology Unit, Santo Spirito Hospital, Casale Monferrato, Italy, ¹⁰Oncology Unit, Villa Scassi Hospital, Genoa, Italy, ¹¹Cancer Epidemiology Unit, Department of Medical Sciences, University of Turin, Turin, Italy, ¹²Cancer Epidemiology Unit, CPO Piemonte, Turin, Italy, ¹³Interdepartmental Center for Studies on Asbestos and Other Toxic Particulates “G. Scansetti”, University of Turin, Turin, Italy, ¹⁴Medical Genetics Unit, AOU Città della Salute e della Scienza, Turin, Italy

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant pleural mesothelioma (MPM) is a rare and aggressive tumor, with median survival time of approximately 12 months and limited systemic therapeutic options. The aim of this study was to evaluate the potential clinical value of DNA methylation (DNAm) in predicting overall survival (OS) as compared to the lymphocyte-to-monocyte ratio (LMR), which is the most used inflammation-based prognostic score in MPM.

**Methods:** We investigated a cohort of 163 incident cases of MPM diagnosed between 2000 and 2010 in the
municipalities of Turin, and Casale Monferrato (Piedmont region, Italy), an area with an exceptionally high incidence of mesothelioma caused by asbestos occupational exposure and contamination in the general environment from the asbestos-cement Eternit plant that was operational until 1986. A genome-wide methylation array (HumanMethylation450 Beadchip) was used to identify novel blood DNA methylation markers related to overall survival in MPM.

Results: Considering 12 months as a cut-off of OS, epigenome-wide association study (EWAS) revealed one statistically significant single-CpG DNA methylation event (P = 7.7 × 10⁻³) detected in a gene on 6p21.31 (adjusting for age, sex, smoke, WBCs estimates and population stratification) after Bonferroni multiple comparisons correction. Kaplan–Meier survival curves highlighted methylation levels at a single-CpG in a gene on 6p21.31 as related to OS (DNA methylation cut-off = 0.45, HR = 2.14, Median Survival = 243 vs 534, days; P = 2.4 × 10⁻³). Stratification by histological subtype and grade were performed to control for any potential disease-related effects.

Conclusion: Our study is the first to demonstrate that a single-CpG DNA methylation event in a gene on 6p21.31 is an independent marker of prognosis in patients with MPM and performs better than LMR inflammation-based scores as prognostic factor. DNA methylation evaluation will enable clinicians to better predict clinically meaningful outcomes and to select patients who are most likely to benefit from specific therapy.

Keywords: Malignant pleural mesothelioma, DNA methylation, survival analysis

P025: Untargeted Metabolomics Discovers Biomarkers in Serum Years Before Mesothelioma Diagnosis: The HUNT Study

Nguyen O¹, Chatzipantsiou C², Lagani V³,⁴,⁵, Markaki M³,⁶, Kvitvang H⁷, Nordborg A⁷, Tsamardinos I³,⁴, Røe O¹,²

¹Norwegian University Of Science And Technology, Department of Clinical Research and Molecular Medicine, Trondheim, Norway, ²Levanger Hospital, Nord-Trøndelag Hospital Trust, Cancer Clinic, Levanger, Norway, ³University of Crete, Department of Computer Science, Heraklion, Greece, ⁴Gnosis Data Analysis PC, Heraklion, Greece, ⁵Iliia State University, Institute of Chemical Biology, Tbilisi, Georgia, ⁶University of Thrace, Department of Molecular Biology and Genetics, Alexandroupolis, Greece, ⁷SINTEF, Department of Biotechnology and Nanomedicine, Trondheim, Norway

Poster Session, Virtual, May 7, 2021

Objectives: To date there are no clinical biomarkers for the early diagnosis of mesothelioma. Early diagnosis is key for effective treatment and survival. In the present study we have analyzed serum samples collected one to sixteen years before diagnosis for identifying metabolomics signatures for the early detection of mesothelioma.

Methods: All serum samples were obtained from the Nord-Trøndelag Health Study (HUNT) Research Centre’s Biobank. Serum samples from 12 individuals that subsequently developed mesothelioma were obtained, as well as from 48 controls. The serum samples were collected in a time frame of one year to sixteen years before diagnosis. All controls were cancer-free at least five years before blood sampling. Furthermore, 12 of the controls were matched to the cases for smoking status (pack years and quit time), gender and age. All subjects were smokers or ex-smokers. Twenty (20) µl of albumin depleted serum samples were profiled with untargeted mass spectrometric metabolomics; analyzed in an UHPLC/ESI-MS/MS system. In total, four different non-targeted LC-MS based methods were developed and used for metabolite analysis in serum. Data pre-processing for metabolite profiling was performed with the xcms and CAMERA R packages. Univariate analysis was performed by using the moderate t-statistic test implemented in the R package Limma, with pairing among samples taken into account with a random effect approach. All analyses were performed with the R statistical software.

Results: A total of 72 significantly differentially expressed metabolites were identified in amide-negative mode, 47 metabolites in amid-positive mode and 42 metabolites in C18-negative mode in cases vs. unmatched controls (adjusted P-value < 0.2; Figure 1A and Figure 1B). When cases were compared to matched controls, 20 significant metabolites were identified to be differentially expressed in amide-negative mode (adjusted P-value < 0.2) with an AUC varying 0.81 – 0.88. The most significant metabolite discriminated mesothelioma patients from their matched controls with an AUC 0.89, and from all controls with an AUC 0.73 (Figure 1C). Eight of these 20 metabolites are
also found among the 72 significant metabolites identified in the same mode in cases vs. unmatched controls with AUC varying 0.73 – 0.84.

**Conclusion:** Our results suggest that metabolic information in serum may help in detecting mesothelioma several years before clinical mesothelioma. To our knowledge, this is the first study conducted on mesothelioma using serum metabolomics in the search of biomarkers for early diagnostic. Further studies are in progress for validation of these findings.

**Keywords:** Mesothelioma, metabolomic, biomarkers, diagnostic, early diagnostic
P026: Blood-based Prognostic Factors in Malignant Pleural Mesothelioma: A Retrospective Analysis

Lauk O1, Greb D1, Opitz I1
1University Hospital Zurich, Department Of Thoracic Surgery, Zurich, Switzerland

Poster Session, Virtual, May 7, 2021

Objectives: According to the current guidelines, patients diagnosed with malignant pleural mesothelioma (MPM) should undergo a multimodality treatment approach consisting of induction chemotherapy, followed by macroscopic complete resection. Until now, adequate patient selection remains the most challenging part. The aim of this study was to validate already established blood-based prognostic markers in our cohort, as well as investigate new prognostic parameters to predict treatment benefit in MPM patients.

Methods: Between March 1999 and December 2017, 227 patients from our prospective database were retrospectively analysed. All patients had histopathological proven MPM and were treated within multimodality therapy approach. The prognostic value of the following blood parameters was analysed before surgical treatment: Haemoglobin, haematocrit, erythrocytes, platelets, white blood cells (WBC), neutrophils, monocytes, eosinophils, basophils, lymphocytes, urea, creatinine, eGFR, albumin, lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), and C-reactive protein (CRP). Not all values were available for each patient. The median was used as a cut-off value for group division. Survival analysis was performed using Kaplan-Meier curves and significance was evaluated by log-rank test.

Results: The median age at surgery was 63 years. 150 patients (66.1%) were treated with EPP, while 77 (33.9%) received P/D. 80.6% of all MPMs were of the epithelioid histotype, while 12.8% and 2.2% were biphasic and sarcomatoid, respectively. The histological subtype was

---

**FIGURE 1** Kaplan-Meier curve of overall survival (OS) in months. A: Haemoglobin (median: 118 g/l, p=0.03). B: WBC (median: 8.67 G/l, p<0.001). C: neutrophils (median: 4.1 G/l, p=0.01). D: eGFR (median 82 ml/min, p=0.04). E: AP (median: 74 IU/l, p=0.01). F: CRP (median: 5 mg/l, p=0.001)
unknown in 4.4% of the cases. IMIG stage (8th edition) was available for 204 patients: 35 Stage IA, 84 Stage IB, 49 Stage II, 30 Stage IIIA, 5 Stage IIIB, and 1 Stage IV. Significant differences in OS were observed for the following biomarkers with poor OS being associated with low haemoglobin (median: 118 g/l, p=0.03), low haematocrit (median: 0.349 l/l, p=0.02), low erythrocytes (median: 3.9 G/l, p=0.01), high WBC (median: 6.67 G/l, p<0.001), high neutrophils (median: 4.1 G/l, p=0.01), low eGFR (median: 82 ml/min/1.73 m2, p=0.04), high AP (median: 74 U/l, p=0.01), and high CRP (median: 5 mg/l, p<0.001).

**Conclusion:** This study validated the prognostic value of previously proposed prognostic factors including haemoglobin, haematocrit, erythrocyte count, WBC, neutrophils, and CRP in a much bigger cohort than described in literature. In addition, eGFR and AP, as representatives of kidney and liver function, respectively, occurred to be significant and may add an additional prognostic value.

**Keywords:** malignant pleural mesothelioma, prognostic values, multimodality treatment, biomarker, blood-based knowledge about the heterogeneity of tumour cells and immune-system/tumour interactions that contribute to patient outcomes.

**Methods:** To characterize the cellular make-up of pleural effusions we performed single cell and whole sample RNA sequencing for three MPM cases. Transcriptome sequencing data from publicly available MPM patient datasets was used to perform confirmatory analyses.

**Results:** We identified heterogeneity in cellular composition and between mesothelioma tumour cells within each patient sample. Tumour heterogeneity comprised three MPM subpopulations indicated by distinct gene expression signatures. Each of the three subpopulations had expression pattern similarities with the three known MPM subtypes, epithelioid, sarcomatoid and biphasic. Publicly available MPM transcriptome data confirmed the concurrent presence of the three mesothelioma cell subpopulations in 66% of samples and two subpopulations in 33% of samples tested. The relative proportion of MPM subpopulations was identified to correlate with patient overall survival. In addition we demonstrated a complex immune microenvironment and a putative cellular interactome dominated by large number of interactions between myeloid and mesothelioma tumour cells.

**Conclusion:** Single cell analysis of effusion samples revealed a complex picture of inter and intra-sample heterogeneity. The different proportions of the three tumour cell subpopulations identified within each sample and the public data could extend our knowledge of the signals that underpin MPM molecular subtyping. Our results provide an overview of the cellular heterogeneity and a complex immune microenvironment in MPM patients that continues to present a challenge for improving patient outcomes.

**P027: Single Cell Sequencing Reveals Three Subpopulations of Mesothelioma Cells**

**Patch A**1, Mukhopadhyay P1, Lee H1, Addala V1, Haque A1, Engel J1, Kazakoff S1, Lee G2,3, Rouse E2,3, Tey S1, Wykes M1, Nones K1, Koufariotis R1, Wood S1, Harvey K4, Powell J5, Pearson J1, Robinson B2,3, Waddell N1, Creaney J2,3

1QIMR Berghofer Medical Research Institute, Herston, Australia, 2National Centre for Asbestos Related Disease, Medical School, University of Western Australia, Nedlands, Australia, 3Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Nedlands, Australia, 4Peter MacCallum Cancer Centre, Melbourne, Australia, 5Institute of Molecular Bioscience, University of Queensland, St Lucia, Australia

**Objectives:** Malignant pleural mesothelioma (MPM) is an aggressive cancer with limited treatment options. Pleural effusions are a common feature of the disease and contain a mixed population of immune and tumour cells. Studying the cell populations within effusions could generate

**Poster Session, Virtual, May 7, 2021**
P028: Breath Analysis Allows Predicting Treatment Response in Malignant Pleural Mesothelioma Patients

Schillebeeckx E1,2, Janssens E1,2, Surmont V3,4, Nackaerts K5, van Meerbeeck J1,2,4,6,7, Lamote K1,2,4

1Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Wilrijk, Belgium, 2Infla-Med Centre of Excellence, University of Antwerp, Wilrijk, Belgium, 3Department of Thoracic Oncology, Ghent University Hospital, Ghent, Belgium, 4Department of Internal Medicine, Ghent University, Ghent, Belgium, 5Department of Respiratory Oncology, University Hospitals KU Leuven, Leuven, Belgium, 6Pulmonology and Thoracic Oncology, Antwerp University Hospital, Edegem, Belgium, 7European Reference Network for rare respiratory diseases (ERN-LUNG)

Poster Session, Virtual, May 7, 2021

Introduction: Malignant pleural mesothelioma (MPM) is an aggressive type of cancer with poor prognosis. After diagnosis, the patient’s response to treatment is assessed by periodical computerized tomography (CT)-scans, which repeatedly expose the patient to radiation. Furthermore, no predictive markers are currently available to predict the optimal therapy regimen for an individual. As volatile organic compounds (VOCs) in exhaled breath have already shown promise as diagnostic markers and can discriminate treatment-naïve patients from those under treatment, we hypothesize that they can also play a role in assessing treatment response of MPM patients.

Objective: Investigate whether VOCs in exhaled breath are able to discriminate treatment outcome in follow-up samples and if so, if this outcome can already be predicted in earlier samples.

Methods: Breath and background samples were collected from 9 MPM patients at inclusion (naïve or under treatment) and follow-up. At least one follow-up sample was available for each participant. Measurements were linked to a CT-scan, which was scored as either stable (SD) or progressive (PD). VOCs were measured via multi-capillary column-ion mobility spectrometry (MCC-IMS). After background correction, a lasso regression was performed to build a discriminative model and select the important discriminatory VOCs, which is visualized by supervised principle component analysis (PCA). A discriminative model was set-up to differentiate between SD and PD in follow-up samples, while a predictive model was trained to predict the follow-up outcome (SD or PD) based on the associated breath sample from the previous study visit. R was used for all statistics.

Results: Patient characteristics are presented in table 1. No significant differences in age, BMI, gender, smoking status and treatment were reported. From a total of 96 VOCs, 8 were selected by the discriminative model and 17 by the predictive model (table 1). With an AUCROC of 0.70, a discrimination between SD and PD in follow-up samples was possible. Furthermore, a prediction of the treatment outcome (SD or PD) based on an earlier breath sample performed even better with an AUCROC of 0.87. The PCA plots clearly visualize the discriminatory capacity of both models (table1). Due to the small samples size, it is to be expected that our confidence intervals are relatively large, which is why we intend on validating these findings in a larger population.

Conclusion: We can conclude that VOCs in exhaled breath are promising in detecting and predicting treatment outcome of MPM patients. However, further research in larger populations is necessary to validate our results.

Volatile organic compounds, Malignant pleural mesothelioma, biomarkers, prediction, breath analysis
### ABSTRACTS

<table>
<thead>
<tr>
<th>N</th>
<th>SD Mean±SD</th>
<th>PD Mean±SD</th>
<th>p-value</th>
<th>N</th>
<th>SD Mean±SD</th>
<th>PD Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>167.93±17.2</td>
<td>194.41±15.4</td>
<td>0.760</td>
<td>5</td>
<td>390.97±37.3</td>
<td>368.91±46.4</td>
<td>0.540</td>
</tr>
<tr>
<td>5</td>
<td>390.97±37.3</td>
<td>368.91±46.4</td>
<td>0.540</td>
<td>5</td>
<td>390.97±37.3</td>
<td>368.91±46.4</td>
<td>0.540</td>
</tr>
<tr>
<td>Gender</td>
<td>50/50</td>
<td>50/50</td>
<td>0.546</td>
<td>50/50</td>
<td>50/50</td>
<td>0.546</td>
<td></td>
</tr>
<tr>
<td>Smoking Status</td>
<td>0/0/0/0</td>
<td>0/0/0/0</td>
<td>0.50</td>
<td>0/0/0/0</td>
<td>0/0/0/0</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Treatment (%)</td>
<td>70/70/70</td>
<td>70/70/70</td>
<td>0.482</td>
<td>70/70/70</td>
<td>70/70/70</td>
<td>0.382</td>
<td></td>
</tr>
</tbody>
</table>

#### Selected ROCs
- P10, P27, P82, P43, P34, P68, P76, P77, P4, P16, P26, P37, P48, P59, P70, P81, P93

#### AUC (%)
- P10, P27, P82, P43, P34, P68, P76, P77, P4, P16, P26, P37, P48, P59, P70, P81, P93

#### Sensitivity (%)
- 50 (50.0-100.0)

#### Specificity (%)
- 50 (50.0-100.0)

#### PPV (%)
- 50 (50.0-100.0)

#### NPV (%)
- 50 (50.0-100.0)

#### Accuracy (%)
- 50 (50.0-100.0)

#### ROC curve

#### Table 1: An overview of the variables, their distribution, and selected peaks and receiver operating characteristics for both models. The principle component analysis plots visualise the discrimination between samples linked to SD and PD (discriminative model) and the discrimination between baseline samples based on treatment outcome (predictive model).


*Mean±SD and BMI with standard deviation.
**P030: Exome-sequencing of Nine Brazilian Mesothelioma**

*Silveira H¹, Evangelista A¹, Andrade E¹, Campanella N¹, Silva E², Dix G³, Vazquez F¹, Reis R¹,⁴,⁵*

¹Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, Brazil, ²Department of Pathology, Barretos Cancer Hospital, Barretos, Brazil, ³Department of Surgery, Barretos Cancer Hospital, Barretos, Brazil, ⁴Life and Health Sciences Research Institute (ICVS), Health Sciences School, University of Minho, Braga, Portugal, ⁵ICVS/3B’s-PT Government Associate Laboratory, Braga/Guimarães, Portugal

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant Mesothelioma (MM) is a cancer rare and highly aggressive malignancy arising in the pleural cavities. The genome profile of MM was recently reported, increasing our biological knowledge of the disease. In this study we performed the exome sequencing of Brazilian MM cases and compared with TCGA and Bueno’s cohorts.

**Methods:** Nine MM from Barretos Cancer Hospital was analyzed, being seven paired blood and tumor tissue and two only tumor tissue. Following DNA isolation, whole-exome sequencing was performed: the DNA libraries were prepared using the Nextera Rapid Capture Custom Enrichment Kit (Illumina, San Diego, CA, USA), cluster generation and sequencing were performed on the Illumina HiSeq 4000. Bioinformatics analysis were performed, MuTect2 was used to call somatic SNVs and indels in tumor-normal pairs and in tumor-only mode. The gnomAD and ABraOM databases and a pool of 291 Brazilian normal patients were used to filter germline variants. Copy number alterations (CNA) were identified using Nexus Copy Number version 10.0. Sanger sequencing analysis was done to confirm specific mutations identified.

**Results:** Of the 9 MM cases, 66.7% were male, with a median age of 57 years, and 75% of them were of epithelioid histology. Exome sequencing revealed a median of 86 variants per sample, being missense the predominant. BAP1 was mutated in 2 cases (22%) cases, that were also confirmed by Sanger Sequencing. Two nonsense mutations were found in NF-2 (22%) (p.Arg198Ter and p.Cys51Ter). Furthermore, TP53 presented 1 missense mutation (p.Ala276Gly). The CNA landscape revealed deletions in suppressor genes CDKN2A and NF-2. CDKN2A losses occurred in 2 samples following MTAP (adjacent gene in the same region 9q21.3). The NF-2 losses happened in 3 cases. On the other hand, BAP-1 analysis was obtained gain in 1 sample and no deletions or losses were demonstrated in our results.

**Conclusion:** Despite of small number of cases analyzed, we identified a similar mutation and CNA profile that reported in the literature, with special emphasis on BAP-1, NF-2 and TP53. Our findings can help for further investigation of biology and novel therapeutics in Brazilian MM patients.

Brazilian mesothelioma exome sequencing BAP-1

---

**P031: The Single Nucleotide Polymorphism rs2235503 C>A Leads to Increased MSLN Gene Transcription and It Is Strongly Associated with the Levels of SMRP In Vivo**

*Silvestri R¹, Pucci P², De Santi C³, Dell’Anno I¹, Miglietta S⁴, Corrado A⁵, Nicoli V⁶, Marolda D¹, Cipollini M¹, Pellegrino E¹, Morani F¹, Evangelista M⁷, Bonotti A⁸, Foddis R⁹, Cristaudo A⁶, Gemignani F¹, Landi S¹*

¹Department of Biology, University of Pisa, Pisa, Italy, ²School of Life Health and Chemical Sciences, The Open University, Milton Keynes, United Kingdom, ³Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland, ⁴San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), IRCCS San Raffaele Scientific Institute, Milano, Italy, ⁵Department of Bioscience, University of Milan, Milano, Italy, ⁶Department of Translational Research and of New Surgical and Medical Technologies, University of Pisa, Pisa, Italy, ⁷Institute of Clinical Physiology (IFC), CNR, Pisa, Italy, ⁸Preventive and Occupational Medicine, University Hospital of Pisa, Pisa, Italy

**Poster Session, Virtual, May 7, 2021**

**Objectives:** The soluble mesothelin-related peptide (SMRP) is generated from the cleavage of mesothelin, a membrane glycoprotein encoded by MSLN gene. High concentrations of SMRP allow a fair discrimination between MPM patients and healthy individuals or subjects affected by other respiratory diseases (“non-MPM”). Thus,
it has become one of the most promising and interesting biomarkers for MPM. However, the diagnostic efficiency of SMRP can be reduced by several confounding factors, including the individual’s genetic background. As shown for other cancer biomarkers, the identification of genetic variants able to affect SMRP levels could lead to an increase of its accuracy by allowing to establish a personalized cutoff based on individual’s genotype. In the present work, we aimed assess association between four variants (haplotypes) of MSLN promoter and SMRP levels in MPM and non-MPM subjects and to identify the single nucleotide polymorphisms (SNPs) functionally responsible for this association.

**Methods:** Blood samples from a cohort of 70 MPM and 689 non-MPM subject were analyzed to assess the association between the SMRP levels and four haplotypic variants of MSLN promoter: haplotype #1 (reference), #2, #3, #4. Functional studies were carried out in Met-5A and Mero14 cell lines using a fluorescence reporter assay. Fluorescence intensity was measured at single cell level with a fluorescence activated cell sorter and used to assess the differences between the activity of the four variants of the MSLN promoter and to identify the SNPs responsible for the observed differences.

**Results:** Carriers of haplotype #2 (characterized by the sequence: rs3764247 C; rs3764246 G; rs2235503 A; rs2235504 G) showed a significantly higher level of SMRP when compared with the reference group (1.30 ± 0.046 nM vs 0.80 ± 0.022 nM; p<10-5). The in vitro functional study supported the in vivo observations since haplotype #2 caused a 41% increase in the reporter fluorescence intensity compared with reference haplotype #1 (p=6x10-4). The in vitro analysis also led to the identification of rs2235503 C>A as the SNP responsible for the increased activity of haplotype #2 (35% increase in the reporter fluorescence intensity; p<10-5).

**Conclusion:** The rare variant of the SNP rs2235503 C>A, specific of haplotype#2, enhances the expression of MSLN gene leading to an increase of SMRP levels in non-MPM subjects. In order to minimize the negative effect of this alteration on the diagnostic performance of SMRP, personalized cutoff values should be established based on individual’s genotype.

**Keywords:** Malignant pleural mesothelioma, soluble mesothelin-related peptide, diagnostic biomarkers, FACS, MSLN
P032: Implementation of a Novel Prospective Database for the Management of Clinicopathological Characteristics for Malignant Pleural Mesothelioma

Tramontozzi P1, Freyaldenhoven S1, Richards W1, Bueno R1

1Thoracic Surgery Oncology Laboratory and the International Mesothelioma Program (www.impmeso.org), Division of Thoracic Surgery, Brigham and Women’s Hospital, and Harvard Medical School, Boston, USA

Poster Session, Virtual, May 7, 2021

Objectives: Every year, approximately 150-200 patients present to the Division of Thoracic Surgery at the Brigham and Women’s Hospital in Boston, USA, with a diagnosis of malignant pleural mesothelioma (MPM). Many patients with MPM enroll in various research protocols involving the collection of tumor specimens. The management of well-annotated clinicopathological information associated with each specimen is crucial for future clinical and translational studies. Our group designed a prospective clinical database to capture a comprehensive record of structured demographic, clinicopathological, and outcome data to support intention-to-treat analyses. In addition, we describe our initial measures to guarantee data integrity.

Methods: A database was designed using the Research Electronic Data Capture (REDCap) platform. With a unique Record ID given to each patient, every record consists of multiple instruments for the collection of Demographic, Pre-Operative, Operative/Pathology, Post-Operative, and Follow-up variables. A relational structured database was implemented to encompass multiple encounters per patient within each appropriate module. The database also allows for redundant data entry for audit purposes. For example, due to the requirement for interpretation of free-text reports, the Operative/Pathology instrument was filled by two different operators independently to assure consensus. In the initial pilot, prospective data was collected by a weekly screen of clinic appointments for patients with a diagnosis of MPM and a consent for specimen collection, while existing records were updated with new Post-Operative and Follow-up data. The internal audit was performed through exporting variables to Microsoft Excel for comparison. Non-matching variables were reviewed by the data manager for root cause analysis and consensus resolution. Time required per data entry was recorded for each module to allow for optimizing workflow.

Results: One hundred patients with collected specimens who presented to clinic between Jan. 2019 and May 2019 were included in the pilot. A total of 103 Demographic, Pre-Operative, and Survival variables were entered per record, with an additional 38 Post-Operative and Follow-up variables updated for every clinical visit. Due to the idiosyncratic clinical course of each patient, double entry for select variables served as feasible manner to ensure accuracy. Sixteen of the Operative/Pathology variables were audited for every record. On average, 14 (87.5%) of the variables were concordant amongst the two entries. The most common discordant variables were “Date of Diagnosis”, “Operation Type/Extent”, “Macroscopic Disease Remaining”, and “TNM Stage”. Eight individuals were involved in the data entry and the average concordance per pairing was also 14 (87.5%) variables. Commonly discordant variables requiring expert interpretation were presented and explained by attending surgeons to allow for closed-loop education of the data entry personnel.

Conclusion: Our database proved to be a manageable and customizable method to collect clinical data. Multiple instruments and conditional branching logic allowed for efficient tailored collection of relevant variables for patients with MPM. Additionally, this multi-instrument relational structure allows for linkage to patient data resident in parallel clinical and genomic databases. In conclusion, we report successful pilot implementation of a flexible, multifaceted, and detailed database to support multidisciplinary MPM research.

Keywords: mesothelioma, prospective database, electronic data capture (EDC)
**P033: Biomarker Discovery Using Multiplex Analytical Techniques Can Improve the Diagnosis, Prognosis and Treatment Monitoring of Mesothelioma**

**Voloca O**, Clench M, Cole L, Haywood-Small S

*Sheffield Hallam University, Sheffield, United Kingdom*

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Current biomarkers in malignant mesothelioma yield variable results as diagnostic and prognostic tools. The main aim of this study is to gain insight into the proteomic profile of immortalised mesothelioma cell lines using multiplex analytical techniques with the prospect of moving towards patient tissue biopsies. This research involves the validation of new and emerging biomarkers using a combination of mass spectrometry, flow cytometry and immunofluorescence techniques to ultimately contribute to the knowledge base surrounding mesothelioma pathogenesis.

**Methods:** Untargeted analysis was completed using liquid chromatography tandem mass spectrometry (LC-MS/MS), a complex and well-established technique in biomarker discovery in recent years. The characteristic proteomic profile of four different cell lines (NCI-H28, MSTO-211H, NCI-H1975 and MeT-5A) was determined using the Waters ™Xevo G2-X2 QTof in positive ion mode and Progenesis QIP software. Targeted analysis was performed using a panel of antibodies including anti-HMGB1, anti-mesothelin and anti-VISTA. For multiparameter flow cytometry, analysis was carried out using a Beckman Coulter CytoFLEX instrument. For immunofluorescence staining, cells were cultured on glass coverslips and images were acquired using a Zeiss LSM800 confocal microscope in airyscan mode.

**Results:** High expression of cytoplasmic HMGB1 in mesothelioma cell lines was confirmed by both flow cytometry and confocal microscopy, consistent with previous reports. Moreover, the preliminary LC-MS/MS proteomic data has identified a new panel of candidate mesothelioma biomarkers, possibly associated with an inflammatory tumour microenvironment.

**Conclusion:** Current experiments are focused on developing a fast and high throughput screening technique for biomarker discovery using LC-MS/MS. Further optimisation of this technique is required prior to validation of patient samples obtained from MesobanK (Cambridge, UK). This targeted analysis supports the hypothesis that novel, more specific biomarkers are required for a robust and facile protein identification method applicable in clinical settings.

**P034: Prognostic Value of Neutrophil-to-lymphocyte Ratio in Patients of Malignant Pleural Mesothelioma Treated with Nivolumab**


*Hyogo College of Medicine, Nishinomiya, Japan*

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Nivolumab, an anti-programmed cell death 1(PD-1) antibody, is a one of standard regimen of the second-line treatment for malignant pleural mesothelioma (MPM). However, compared with molecular-targeted drugs, the response rate to nivolumab is low, and biomarkers of efficacy are currently lacking. It has been recently reported that the neutrophil-to-lymphocyte ratio (NLR) can be a biomarker of efficacy of nivolumab for lung cancer. Here, we examined the possibility for NLR to predict efficacy of nivolumab for MPM.

**Methods:** We retrospectively examined all patients with MPM who were treated with nivolumab at our institution.

**Results:** We compared 34 patients with NLR of ≥3.5 and 31 with NLR of <3.5, all of whom were treated with nivolumab. The response rate (RR) was 14.7% in the NLR≥3.5 group, and 25.8% in the NLR<3.5 group. The median (m) PFS and mOS were 93 and 343 days in the NLR≥3.5 group, whereas those were 169 days and not reached (NR) in the NLR<3.5 group. There were no significant differences of RR, PFS, and OS between this two groups, but there were the trend of better RR and longer survivals were observed in the NLR<3.5 group than in the NLR≥3.5 group.

**Conclusion:** It was suggested that NLR may be a predictive marker of the effect of nivolumab for MPM.

**Keywords:** nivolumab NLR
P035: The Landscape of Copy Number Alterations Detected by Digital MLPA in Malignant Mesothelioma

Yoshikawa Y, Ohmuraya M, Emi M, Carbone M

1Hyogo College of Medicine, Nishinomiya, Japan, 2University of Hawai’i Cancer Center, Honolulu, USA

Poster Session, Virtual, May 7, 2021

Objectives: In order to detect segmental chromosomal alterations comprehensively in malignant mesothelioma (MM), a high-throughput technique, digital MLPA (Multiplex Ligation-dependent Probe Amplification), was established to detect CN alterations in high sensitivity and reproducibility. The purpose of this research is to utilize characteristic chromosomal alterations as a biomarker of MM.

Methods: DigitalMLPA is the combined technology with MLPA and NGS. Target genes are 234 genes; the probemix D017 (X1-1018) included i) 150 target probes for 10 genes having frequent mutations in MM; ii) 223 reference probes hybridizing to copy number stable regions for karyotyping; and iii) 78 internal control probes for sample identification, and 53 probes for quantity and quality assessment. The target genes evaluated by multiple probes were 10 genes: BAP1, SETD2, SMARCC1, PBRM1, VHL, TP53, CDKN2A, CDKN2B, NF2, and HCFC1. Total 64 MMs (17 cell lines, 11 primary culture cells, 36 tumor tissues) were analyzed.

Results: About 1/3 of MMs showed the chromothripsis-like patterns (CTLP) in at least one region of 3p21 (SETD2, BAP1), 9p21.3 (CDKN2A/2B), 17p13.1 (TP53), or 22q12.2 (NF2) and most cases had the combinatorial CN losses of these genes. Exon-based CN alterations in TP53 was shown in figure 1. Furthermore, deletions of Chr 4q, 13q, 14q, and 18q, and amplification of Chr 5p, 7p, 8q, 19, 20q were frequently detected.

Conclusion: In clear cell renal cell carcinoma with one allelic loss and loss-of-function mutation of BAP1 gene, segmental CN alteration accompanying biallelic deletion was quite rare except for CDKN2A/2B gene. MMs demonstrated CTLP in many chromosomes simultaneously and it would be characteristic for MMs.

Malignant mesothelioma, Copy-number, chromothripsis-like patterns, digitalMLPA
P036: Serum Calretinin as a Biomarker in Asbestos-Related Diseases

Zupanc C1, Franko A2, Štrbac D3, Dodič Fikfak M2, Kovač V4, Dolžan V4, Goričar K4

1University Medical Centre Ljubljana, Ljubljana, Slovenia, 2Clinical Institute of Occupational Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia, 3Institute of Oncology Ljubljana, Ljubljana, Slovenia, 4Pharmacogenetics Laboratory, Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, University of Ljubljana, Slovenia

Poster Session, Virtual, May 7, 2021

Objectives: Early diagnosis of malignant mesothelioma (MM) could improve the treatment and prognosis of MM patients. To confirm MM diagnosis, immunohistochemical analysis of several markers, including calretinin, on tissue samples is currently required. In this study, our aim was to evaluate serum calretinin as a potential minimally invasive biomarker in asbestos-related diseases, especially in MM.

Methods: We included in our study 549 subjects: 164 MM patients, 117 subjects with asbestosis, 195 subjects with pleural plaques, and 73 subjects that were occupationally exposed to asbestos, but did not develop any asbestos-related disease. Serum calretinin concentration was determined with commercially available enzyme immunoassay (Calretinin ELISA, DLD Diagnostika GmbH, Germany). Non-parametric tests and ROC curve analysis were used for statistical analysis.

Results: Serum calretinin concentration differed significantly among subject groups (P<0.001): it was 0.52 (0.23-1.43) ng/ml in MM patients, 0.13 (0.08-0.2) ng/ml in subjects with asbestosis, 0.18 (0.12-0.25) ng/ml in subjects with pleural plaques, and 0.12 (0.07-0.2) ng/ml in subjects without asbestos-related diseases. MM patients had statistically significant higher calretinin concentration than subjects without disease, subjects with pleural plaques or subjects with asbestosis (all P<0.001). Calretinin concentration was also significantly higher in subjects with pleural plaques than in subjects without disease (P=0.003) or asbestosis (P=0.005).

In ROC curve analysis comparing MM patients with all other subjects, the area under the curve for calretinin concentration predicting MM was 0.826 (95% CI=0.782-0.869; P<0.001). At the cutoff value of 0.32 ng/ml, sensitivity for predicting MM was 0.683, while specificity was 0.886.

Among clinical characteristics of MM patients, only histological type was significantly associated with serum calretinin (P=0.001). Calretinin concentration was 0.67 (0.30-1.66) ng/ml in epithelioid type, 0.51 (0.20-1.17) ng/ml in biphasic, and 0.17 (0.13-0.23) ng/ml in sarcomatoid MM. Patients with sarcomatoid MM had significantly lower calretinin than patients with epithelioid type (P=0.001) and tended to have lower calretinin compared to patients with biphasic MM (P=0.057). Patients with peritoneal MM tended to have even higher serum calretinin (1.00 (0.40-2.41) ng/ml) compared to patients with pleural MM (0.48 (0.22-1.27) ng/ml), but the difference did not reach statistical significance (P=0.065).

Conclusion: Our study suggests serum calretinin could serve as a diagnostic marker differentiating between MM and other asbestos-related diseases. The results could contribute to the earlier diagnosis of MM and to a better understanding of various asbestos-related diseases.

P037: Retrospective Evaluation of the Use of Pembrolizumab in Malignant Pleural Mesothelioma in a Real World Australian Population

Ahmadzada T1, Cooper W1,2,3, Holmes M1, Mahar A2, Westman H4, Gill A1,5, Nordman I6,7, Yip P8,9, Pal A10, Zielinski R11,12, Pavlakis N13, Nagrial A1,14, Daneshvar D15, Brungs D16,17, Karikios D1,18, Aleksova V19, Burn J20, Asher R21, Grau G1,22,23, Hosseini-Beheshti E1,22, Reid G1,24, Clarke S1,13, Kao S1,19,25

1Sydney Medical School, The University of Sydney, Camperdown, Australia, 2Royal Prince Alfred Hospital, Camperdown, Australia, 3School of Medicine, Western Sydney University, Sydney, Australia, 4Northern Sydney Cancer Centre, Royal North Shore Hospital, Sydney, Australia, 5Cancer Diagnosis and Pathology Group, Kolling Institute of Medical Research, Royal North Shore Hospital, Sydney, Australia, 6Department of Medical Oncology, Calvary Mater Newcastle, Newcastle, Australia, 7University of Newcastle, Newcastle,
**Poster Session, Virtual, May 7, 2021**

**Objectives:** The PROMISE-Meso phase 3 trial recently demonstrated a superior response rate for pembrolizumab in malignant pleural mesothelioma (MPM) patients when compared to chemotherapy in the second line setting, but not in progression free survival (PFS) and overall survival (OS). This underlines the importance of finding clinical factors and predictive biomarkers to select for patients that are likely to benefit from pembrolizumab. We aimed to determine the “real-world” efficacy and toxicity of pembrolizumab in MPM patients and to investigate predictive tumour biomarkers potentially associated with response to pembrolizumab.

**Methods:** MPM patients who were treated with pembrolizumab as part of the iCARE NSW compensation scheme were included. Clinical information was collected retrospectively. Survival analyses were performed using Kaplan Meier test for OS and PFS. Tumour biomarkers such as programmed death-ligand 1 (PD-L1; E1L3N clone), BAP1 (C-4 clone) and tumour infiltrating lymphocytes (TILs; CD3+; LN10 clone) were examined using archival formalin-fixed paraffin-embedded tumour samples.

**Results:** A total of 98 patients were included: median age 70 years (range, 46-91); 92% male; 76% epithelioid subtype; 78% Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1. Pembrolizumab was used as second or subsequent line treatment in 94 patients and as first line treatment in 4 patients. The overall response rate was 18% and the disease control rate was 56%. The median PFS was 4.89 months (95% CI: 3.75-6.40) and the median OS was 9.5 months (95% CI: 6.64-13.67). Immune-mediated adverse events occurred in 27% of patients, with 7 patients (7%) having had G3 toxicities including myasthenia gravis, nephritis, pneumonitis and scleroderma.

Absence of dexamethasone pre-treatment was independently associated with better OS (median OS: 10 vs 3 months, p<0.01). Factors independently associated with better PFS included age ≥65 (median PFS: 6 vs 5 months, p=0.04), ECOG status 0 (median PFS: 12 vs 4 months, p<0.01), and occurrence of immune-related adverse events (median PFS: 9 vs 4 months, p<0.01).

PD-L1 expression and BAP1 expression were assessed in 54 patients so far: 37% with PD-L1≥1%; 31% with PD-L1≥5%, 6% with PD-L1≥50% and 39% had BAP1 loss. TILs were assessed in 55 patients so far: 27% had ≥10% TILs in the stroma. PD-L1 expression (≥1%), BAP1 loss and TILs (≥10%) in the stroma were not significantly associated with OS, PFS nor with ORR.

**Conclusion:** Our real-world efficacy data in patients receiving pembrolizumab as second or subsequent line therapy are comparable to the results from the recent PROMISE-Meso trial. Factors such as older age, good performance status and occurrence of immune-related adverse events were associated with longer PFS following pembrolizumab treatment, while absence of dexamethasone pre-treatment was associated with longer OS. In analyses to date, positive PD-L1 expression, BAP1 loss and presence of TILs were not associated with any efficacy outcomes. More patients will be analysed and will be included for presentation at the conference.
P038: A Multicenter Randomized Phase III Trial of Dendritic Cells Loaded with Allogeneic Tumor Cell Lysate (MesoPher) in Mesothelioma Patients as Maintenance Therapy after Chemotherapy; Denim-trial

Belderbos R1,2, Baas P3, Berardi R2, Cornelissen R1,2, Fennell D5, van Meerbeeck J4, Scherpereel A6, Vroman H1,2, Aerts J1,2

1Erasmus Medical Center, Rotterdam, Netherlands, 2Erasmus MC Cancer Institute, Rotterdam, Netherlands, 3Netherlands Cancer Institute, Amsterdam, Netherlands, 4University Hospital Antwerp, Antwerp, Belgium, 5University of Leicester, Leicester, United Kingdom, 6Centre Hospitalier Régional Universitaire de Lille, Lille, France, 7Università Politecnica delle Marche - Ospedali Riuniti di Ancona, Ancona, Italy

Poster Session, Virtual, May 7, 2021

Objectives: Malignant Pleural Mesothelioma (MPM) is an aggressive, treatment recalcitrant neoplasm. Current treatment first line treatment, consisting of a combination of antifolate and platinum-based chemotherapy, results in an overall survival of 9-12 months from start of therapy. Checkpoint inhibitor treatment has not yet proven to be superior over second-line chemotherapy for improving overall survival. The disappointing clinical results could be correlated to low numbers of tumor-infiltrating CD8+ T-cells in MPM patients. Dendritic cell (DC) therapy can instigate an immune response and activate tumor-specific CD8+ T-cells. Allogeneic tumor-lysate loaded DC therapy has proven to be effective in mice and safe and feasible in humans. We have initiated a randomized, phase 2/3, multicenter, open-label trial to examine the efficacy of DC therapy in humans with histologically proven MPM (fig 1.).

Methods and Results: In this open-label, multicenter phase III trial patients are randomized to receive either DC therapy plus Best Supportive Care (BSC) or BSC only according to the discretion of the local investigator after first line chemotherapy treatment. The primary end point is overall survival. The secondary endpoints will be safety and tolerability, progression-free survival, overall response rate and quality of life. Immunomonitoring will be done as part of the exploratory analysis. 230 patients are planned to be enrolled in the trial. Study enrollment started at May 2018 and inclusion is expected to be completed in the fourth quarter of 2020. The independent data safety monitoring board last reviewed the trial in February 2019 and suggested that the trial continues as planned.

Conclusion: This Phase III trial will determine whether DC therapy in patients with MPM is effective as a maintenance treatment after chemotherapy and may be a new treatment option for MPM.

Keywords: dendritic cell-based therapy, mesothelioma, immunotherapy, clinical trial
P039: A Trial of Intra-Pleural bacterial immunoTherapy in Malignant Pleural Mesothelioma (TILT) – A Randomised Feasibility Study Using the Trial Within a Cohort (TwiC) Methodology

Bibby A1, Zahan-Evans N1, Keenan E1, Comins C2, Harvey J, Day H, Rahman N3, Fallon J4, Gooberman-Hill R5, Maskell N1

1Bristol Academic Respiratory Unit, Bristol, United Kingdom, 2Bristol Haematology & Oncology Centre, Bristol, United Kingdom, 3Oxford Respiratory Trials Unit, Oxford, United Kingdom, 4Musgrove Park Hospital, Somerset NHS Foundation Trust, Taunton, United Kingdom, 5NIHR Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, Bristol, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: Systemic immunotherapy has been shown to be effective front-line treatment for malignant pleural mesothelioma (MPM). However, immunotherapy is associated with side effects, which may deter some patients. Delivering therapeutic agents directly into the pleural space can decrease systemic drug absorption and reduce the risk of side effects. Intra-pleural immunotherapy is supported by a valid scientific rationale and there is a long history of administering bacterial immune-stimulants via this approach. The TILT trial investigated the feasibility of a randomised trial of intra-pleural bacterial immunotherapy in people with MPM, using an innovative and highly pragmatic methodology called trials within cohorts (TwiC).

Methods: TILT was a multi-centre, three-armed, randomised, feasibility TiwC of intra-pleural OK432 (streptococcus pyogenes), BCG or usual care in people with MPM, who were not currently receiving chemotherapy. Eligible participants were identified within the ASSESS-meso study; a prospective, longitudinal, observational cohort study. The primary outcomes were feasibility, evaluated against pre-specified recruitment, attrition and data completeness targets, and acceptability, assessed during qualitative interviews with participants and family members at the end of the trial. Secondary outcomes included adverse events, survival, radiological response rates, pleurodesis and serological parameters including mesothelin.

Results: The recruitment target was 12, however just seven people enrolled, and the 66% recruitment rate target was not met. Additionally, two participants withdrew after randomisation, breaching the pre-stated attrition threshold of 10%. The main factor affecting recruitment was the small number of patients meeting the eligibility criteria, specifically the requirement to have an indwelling pleural catheter with underlying expandable lung (Figure 1). Several recipients of intra-pleural bacterial agents experienced severe local and systemic inflammatory responses, with one participant requiring a prolonged course of oral steroids to control their symptoms. Blood tests reflected these reactions with increased CRP and platelets observed in the intervention arm after drug administration. There was no difference in radiological response rates or survival between arms. However, median survival for the whole trial population was 21.0 months (IQR 8.9-29.0) with a 1-year survival rate of 71.4% (5/7), implying potential selection bias.

Conclusion: The TwiC design was successfully applied to a clinical drug trial and was found to be acceptable to participants and relatives. However, the trial was not a feasible method of investigating intra-pleural bacterial immunotherapy in people with MPM, mainly due to recruitment difficulties and eligibility constraints. Future intra-pleural therapy trials should be aware of these challenges, and of the adverse reactions associated with intra-pleural bacterial immunotherapy.

Pleural mesothelioma, Immunotherapy, Intra-pleural therapies, Pragmatic trials, Feasibility trial
Figure 1 - Flow chart demonstrating participant screening, eligibility, and enrolment in TILT.
P040: Exploring the Barriers Faced by Mesothelioma Patients When Accessing Clinical Trials in the UK

Bolton S¹

¹Mesothelioma UK, Leeds, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: Cases of mesothelioma in the UK continue to rise. New data from HSE showed 2,595 deaths from mesothelioma compared with 2,542 deaths in 2015.

The National Institute for Health Research has increased research activity since its inception in April 2006 by providing infrastructure within NHS organisations to support research activity in NHS organisations. Despite this, figures for patients taking part in mesothelioma research vary across the country. A review of all patients diagnosed with mesothelioma in Yorkshire in 2015 showed only 14% of patients enrolled in a clinical trial with just 4 out of 97 patients entered a clinical trial where active systemic therapy formed one arm of the trial. The National Mesothelioma Audit Report 2018 doesn’t provide data on trial entry yet one of the 12 key recommendations of the report states “All patients should be offered access to relevant clinical trials even if this requires referral outside of their network”.

Locally, an informal scoping exercise among patients, carers and healthcare professionals in Yorkshire revealed a sense of frustration about access to mesothelioma research. Participants reported that it was difficult to find out about research opportunities and access to clinical trials. This included frustrations about how decisions are made about access to research opportunities. People also discussed the type of research that is undertaken, mechanisms for people getting access to research and access to research findings which inform treatment.

This aim of this study is to explore research access for people with mesothelioma in a more systematic way. The study will test and expand on the initial scoping exercise.

Methods:

Part 1: Questionnaire Study

A qualitative questionnaire will be developed with the aid of the members of the MESSothelioma Support Yorkshire (MESSY) group. This will allow free text options to gain an understanding of the major themes.

Identification of participants:

• Patients

Patient will be identified through the Lung / Mesothelioma CNS working in each of the 7 Hospital Trusts within the West Yorkshire and Harrogate Cancer Alliance region.

• Carers

• Health Care Professionals (HCP)

Identified as core members of each of the regions lung cancer MDTs.

All participants will be provided with paper and electronic access to questionnaire.

Part 2: Interview Study

Aim to conduct 27 interviews (9 patients; 9 carers and 9 HCPs over a 6 month period conducted by three researchers. There will be flexibility on the interview location to ensure inclusivity of participants at all stages of their pathway.

Interviews will aim to be 45 minutes in duration.

Part 3: Data Analysis and Report writing

Results: The team have been awarded a £10K research grant from the Mavis Nye Foundation to undertake this important study. The questionnaire & interview process is expected to begin in 2020.

Conclusion: This study will provide healthcare professionals with a better understanding of research barriers faced by patients with mesothelioma and improve access to clinical trials for those affected by mesothelioma.
P041: Gene Expression Analysis Results From a Phase 2 Trial of Durvalumab With First Line Chemotherapy in Malignant Pleural Mesothelioma (DREAM)

Cook A1,2, Yip S5,6, Kok P4, Brown C5,6, Stockler M5,6, Lesterhuis J1,2,4, Nowak A1,2,3

1University of Western Australia, Perth, Australia, 2National Centre for Asbestos Related Disease, Perth, Australia, 3Sir Charles Gairdner Hospital, Perth, Australia, 4Telethon Kids Institute, Australia, 5NHMRC Clinical Trials Centre, Australia, 6University of Sydney, Sydney, Australia

Poster Session, Virtual, May 7, 2021

Background: The single-arm, phase 2 DREAM study was designed to determine the activity, safety and tolerability of durvalumab, cisplatin and pemetrexed as first line therapy in Malignant Pleural Mesothelioma. The study met its primary endpoint, with 54% of 54 patients alive and progression free at 6 months, partial responses in 48% of participants, a median progression free survival of 6.9 months (95% CI 5.5-9.0) with a median overall survival of 18.4 months (95% CI 13.1-27). Here we report initial results from gene expression analysis of tumour biopsy samples collected from the DREAM trial.

Methods: Archival formalin-fixed paraffin-embedded (FFPE) tumour samples, from diagnostic biopsies collected from 54 DREAM study participants, were assessed for RNA expression using the nanoString technology platform. Glass slides with 5 µm sections, approximately 8 per patient, were processed using the Roche FFPE RNA extraction kit. Extracted RNA was assessed quantitatively and qualitatively by bioanalyzer, and samples passing recommended QC thresholds were then processed in accordance with the instructions for the nCounter PanCancer IO 360 kit. Patient samples were run on an nCounter SPRINT instrument, in batches of 11 in parallel with a reference sample. Downstream analysis was performed using nSolver 4.0 software. Expression of 770 target genes was analysed, and normalised using comparative expression of internal reference genes within each sample.

Results: Tumour tissue was available from 51 participants. We will present the results of gene expression analysis of the 700+ immune-oncology related genes, correlated with patient outcomes such as progression free survival (PFS), overall survival (OS), duration of response, and prognostic or predictive biomarkers with respect to which patients did or did not respond to treatment. Data on concordance of PD-1 and PD-L1 between gene expression analysis and IHC staining analysis will also be presented.

Conclusions: Data will be summarised and fully discussed following completion of analysis.

P042: Real-life Data of Nivolumab in Patients with Recurrent Malignant Pleural Mesothelioma. Data from Expanded Access Program in Two Tertiary Cancer Centers in the Netherlands

de Gooijer C2,3,4, Belderbos R2,3, de Gooijer C1, Dumoulin D2,3, Cornelissen R2,3, Burgers J1, Baas P1, Aerts J2,3

1Department of Pulmonary Medicine, Erasmus MC, Rotterdam, The Netherlands, 2Department of Thoracic Oncology, Erasmus Cancer Institute, Amsterdam, Netherlands, 3Erasmus MC Cancer Institute, Erasmus MC Rotterdam, Rotterdam, The Netherlands, 4Clinica Oncologica, Università Politecnica delle Marche, AOU Ospedali Riuniti, Ancona, Italy

Poster Session, Virtual, May 7, 2021

Objectives: Standard treatment options for patients with recurrent malignant pleural mesothelioma (MPM) after first line chemotherapy are lacking. Nivolumab, an anti-PD-1 (monoclonal antibody), showed promising results in small phase II trials in pre-treated MPM patients. However, these trials were performed in small, highly selected patients populations. Furthermore, data from the PROMISE-meso randomized phase III trial (NCT02991482), comparing PD-1 inhibitor pembrolizumab, to single arm chemotherapy as second line treatment, failed to show superiority of anti-PD-1 mAb. The aim of the study was to describe the clinical outcome of pre-treated MPM patients receiving nivolumab in a real life setting.

Methods: Since October 2017, nivolumab was provided for patients with MPM by BMS in the Expanded Access Program (EAP) in the Netherlands. We performed a
retrospective cohort study from all 135 MPM patients enrolled at the Erasmus Medical Center (Rotterdam, NL) and The Netherlands Cancer Institute (Amsterdam, NL) in the EAP for nivolumab. Patients were eligible if they had progressive disease after at least one line of chemotherapy; a good clinical performance score at time of screening (ECOG 0-1); adequate lab values; no autoimmune disease and no treatment with systemic steroids (>10 mg/day prednisone equivalents). Patients were treated biweekly with nivolumab 3mg/kg independent of PD-L1 expression. CT scan evaluation was performed every 6-12 weeks, using modified RECIST for malignant mesothelioma incorporated with the immune RECIST regarding pseudoprogression and confirmation of response.

**Results:** In the full cohort of 107 patients who were eligible for the analysis, the median progression-free survival (PFS) was 2.3 months (95% CI: 1.6–2.9) and the median overall survival (mOS) was 6.7 months (95% CI: 6.2–10.0). The disease control rate (DCR) at 12 weeks was 37% and the objective response rate (ORR) was 10%. PFS was also similar among patients with non-epithelioid and epithelioid histology (log-rank P value 0.89). Patients with positive PD-L1 status (≥1%) showed an improved ORR (36% vs. 9%, P value 0.05), without a PFS nor an OS benefit.

**Conclusion:** Our study showed that response rate and survival were lower in our real-world database compared to those of small phase II clinical trials. Neither pathological subtype nor PD-L1 status were able to predict clinical benefit of nivolumab in MPM patients.

**Keywords:** Checkpoint inhibition, Mesothelioma, Immunotherapy

---

**P043: PEMbrolizumab Plus Lenvatinib In Second Line And Third Line Malignant Pleural Mesothelioma Patients: A Single Arm Phase II Study (PEMMELA)**

de Gooijer C\(^1\), de Vries J\(^1\), Schilder B\(^1\), Monkhorst K\(^1\), Lalezari F\(^1\), Vermeulen M\(^1\), van der Noort V\(^1\), Thommen D\(^1\), Burgers J\(^1\)

\(^1\)Netherlands Cancer Institute, Amsterdam, Netherlands

**Objectives:** Although systemic therapy is the standard treatment for unresectable malignant pleural mesothelioma (MPM), no effective second line treatment for this rare malignancy has been revealed. Pembrolizumab showed to be active in small phase II studies in MPM. However, its efficacy was not confirmed in a randomized controlled trial (gemcitabine or vinorelbine vs pembrolizumab; PROMISE-meso). So, new drug combinations are needed which exhibit a synergistic interaction with pembrolizumab to improve its efficacy in MPM. The broad spectrum of targets of lenvatinib predicts a synergistic interaction with PD-1 blocking. The aim of this study is to characterize the potential activity, toxicity and biomarkers of outcome of pembrolizumab - lenvatinib in patients with recurrent MPM.

**Methods:** PEMMELA is a Dutch prospective single center, single arm, open label, investigator-initiated phase II trial for patients with unresectable malignant pleural mesothelioma who have progression or a recurrence after 1 or 2 lines of chemotherapy. Key eligibility criteria are measurable disease according to Modified RECIST 1.1 for malignant pleural mesothelioma (mRECIST), no previous treatment with immunotherapy or an angiogenesis inhibitor and an Eastern Cooperative Oncology Group performance status 0 or 1. Patients will receive intravenous pembrolizumab (200mg Q3W) and orally lenvatinib (20mg QD) which can be adapted based on adverse events. Treatment is continued for up to 2 years or until confirmed progression or unacceptable toxicity. A biopsy of the pleura will be taken before the first gift of study medication and after 6 weeks of treatment. The sample size is estimated based on the primary endpoint objective response rate (ORR) by mRECIST. Thirty-six evaluable patients (all patients who have received at least one cycle of therapy and have at least one response evaluation) will be recruited to test the hypothesis that combination therapy will improve the ORR from 20% to 40%. The null hypothesis that the true response rate is 20% will be rejected if 11 or more of the 36 patients have an objective response, with a nominal 1- sided type α of 0.10 and power of 0.91. Subgroup analyses will be performed to assess both the correlation between PD-L1 status (22C3)- and pathological subtype, and ORR. Main secondary endpoints are the ORR by an independent radiologist, the disease control rate, (progression free) survival and safety. Translational research will focus on the immunological effect of the combination therapy by exhale breath...
analyses, peripheral blood analyses and longitudinal tumor biopsies. Funding: Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc. This trial is registered at ClinicalTrials.gov, number NCT04287829.

Results: Registration of the first study-patients is planned for February 2021.

Conclusion: This trial will examine the added value of lenvatinib to pembrolizumab in patients with unresectable malignant pleural mesothelioma who have progression or recurrent disease after 1 or 2 lines of chemotherapy.

P044: Phase II Study of Nivolumab and Ramucirumab for Patients with Previously Treated Mesothelioma: Hoosier Cancer Research Network LUN15-299

Dudek A1, Chiappori A2, Rolfo C3, Mamdani H4

1HealthPartners, SAINT PAUL, United States, 2Moffitt Cancer Center, Tampa, United States, 3University of Maryland, Baltimore, United States, 4Karmanos Cancer Center, Detroit, United States

Poster Session, Virtual, May 7, 2021

Objectives: Anti-angiogenic therapy in conjunction with standard platinum and anti-folate chemotherapy has been shown to be effective in malignant mesothelioma in the front-line setting. While there is no standard second line therapy for mesothelioma, therapy with immune checkpoint inhibitors have shown promise in this setting. There is now a plethora of preclinical and clinical data showing an interaction between immune response and tumor angiogenesis. The PD-L1 and VEGFR2 are highly expressed on mesothelioma cells and are therefore attractive targets for treatment of this cancer. We therefore hypothesized that combination of ramucirumab, a human monoclonal antibody targeting VEGFR2, and nivolumab, an antibody targeting PD-L1, can have synergistic activity in previously treated mesothelioma.

Methods: This is an open-label, single stage phase 2 trial. Patient population: patients with histologically confirmed, unresectable mesothelioma, that progressed on at least one pemetrexed-containing regimen and with adequate hepatic, renal, and bone marrow function, and ECOG performance 0 or 1 at the screening. Treatment regimen consists of ramucirumab 8 mg/kg and nivolumab 240 mg, both given intravenously every 14 days until disease progression or intolerable toxicity.

The primary endpoint is the response rate [complete response (CR) + partial response (PR)] of patients for the therapy. A previous study identified a response rate of 20% for pembrolizumab, an anti PD-1 agent, in patients with malignant mesothelioma. We hypothesize a response rate of 40%. Controlling for a probability of Type I error at 0.05 (one-sided), our sample size is estimated to be 33 to ensure 80% statistical power in successfully detecting an alternative response rate of 0.40, compared to a null rate of 0.2. With estimated up to 15% of patients that are not assessable for primary endpoint, sample size will be increased to 35.

Secondary endpoints are progression free survival, overall survival (OS), and toxicity of ramucirumab and nivolumab combination. Exploratory endpoints are expression of PD-L1 in tumor tissue, cytokine expression in tumor tissue, level of soluble PD-L1 in serum, and CD 8+, granzyme B expressing T cells infiltration of tumor, before and during therapy, and their correlation with best clinical responses. This study is currently enrolling patients (ClinicalTrials.gov Identifier: NCT03502746).

Keywords: previously treated mesothelioma, nivolumab, ramucirumab, phase 2 study

P045: Radiological Responses in the STELLAR Trial: Tumor Treating Fields Plus Chemotherapy for First-line Malignant Pleural Mesothelioma (MPM)

Tiku K1, Ceresoli G2

1SS Antonio e Biagio Hospital, Alessandria, Italy, 2Cliniche Humanitas Gavazzeni, Bergamo, Italy

Poster Session, Virtual, May 7, 2021

Objectives: Tumor Treating Fields (TTFields) are an anti-mitotic, regional treatment modality, utilizing low intensity
Alternating electric fields delivered non-invasively to the tumor. TTFields have significantly extended survival of patients with glioblastoma. In-vitro, human MPM cells were highly susceptible to TTFields. In the Phase 2 STELLAR trial (Ceresoli et al. Lancet Oncol 2019), patients with unresectable MPM treated with first line chemotherapy in combination with TTFields had a promising median overall survival of 18.2 months. Median progression-free survival was 7.6 months. One- and 2-year survival rates were 62.2% and 41.9%, respectively. The current sub group analysis describes the characteristics of responders and the pattern of response in the evaluable population (patients with at least 1 CT scan after baseline per mRECIST).

Methods: The STELLAR trial accrued 80 patients with unresectable, previously untreated MPM. Patients received continuous 150 kHz TTFields (>18h/day) combined with pemetrexed and cisplatin or carboplatin (standard dosing). Inclusion criteria comprised ECOG PS of 0-1, pathologically proven MPM and at least one measurable or evaluable lesion per modified RECIST criteria. Patients were followed q3w (CT scan q6w) until disease progression. Radiological assessments were done 6-weekly at study sites.

Results: 72 patients in the trial had at least one follow-up CT scan and were therefore evaluable for response according to mRECIST criteria. Partial responses (PRs) were seen in 40% (29/72) of evaluable patients and clinical benefit (PR+SD) was seen in 97% (70/72) patients. The median time between treatment start and PR was 1.9 months (range: 1.4-4.4 months). Median PFS in the responders was 9.1 months vs 7.6 months in ITT population. All patients presenting with PR during the STELLAR study had continuous reduction in the total sum of lesion diameters, suggesting no initial/pseudo-progression. 83% of the patients who responded to the combined therapy finally had disease progression with a median response duration of 5.7 months (range: 1.4-13 months). One patient did not progress for more than 27 months. 28 responders (97%) reported at least 1 AE, and 25 patients (86%) had TTFields-related skin toxicities. Median compliance of responders to TTFields for first 3 months was 70% (16.8 hours/day); ITT compliance was 68% (16.3 hours/day).

Conclusion: Radiological responses and disease control rates were seen in 40% and 97% of patients in the STELLAR trial. The only TTFields-related AE was skin irritation beneath the arrays. TTFields in combination with pemetrexed and platinum chemotherapy was a safe and active treatment for unresectable, previously untreated MPM. The FDA recently approved TTFields in combination with chemotherapy for first-line treatment of MPM.

P046: TALAMESO: A Phase II Trial to Assess the Efficacy of Maintenance Treatment with Talazoparib Following First Line Platinum-based Chemotherapy in Pleural and Malignant Peritoneal Mesothelioma

Villeneuve L1, Lopez J3, Rousset P2,4, Isaac S2,5, Locatelli-Sanchez M6, Pinson S1, Bin-Dorel S8, Villeneuve L2,8, Schwertz V9, Roche S10, Maucort-Boulch D10, You B2,11

1Service de Chirurgie Digestive et Endocrinienne, Hôpital Lyon Sud, Hospices Civils de Lyon, Lyon, FRANCE, 2EMR 3738 CICLY, Université Lyon 1, Lyon, FRANCE, 3Plateforme BIOGENET Sud, Service de Biochimie et Biologie moléculaire, Hôpital Lyon Sud, Hospices Civils de Lyon, Lyon, FRANCE, 4Service de Radiologie, Hôpital Lyon Sud, Hospices Civils de Lyon, Lyon, FRANCE, 5Service d’Anatomie et Cytologie Pathologiques, Hôpital Lyon Sud, Hospices Civils de Lyon, Lyon, FRANCE, 6Service de Pneumologie et Cancérologie Thoracique, Hôpital Lyon Sud, Hospices Civils de Lyon, Lyon, FRANCE, 7Service de Radiologie, Hôpital Lyon Sud, Hospices Civils de Lyon, Lyon, FRANCE, 8Unité de Pharmacie Clinique et Biostatistiques, Pôle de Santé Publique, Hospices Civils de Lyon, Lyon, FRANCE, 9Service de Recherche et Epidémiologie Cliniques, Pôle de Santé Publique, Hospices Civils de Lyon, Lyon, FRANCE, 10Service de Biostatistiques, Pôle de Santé Publique, Hôpital Lyon Sud, Hospices Civils de Lyon, Lyon, FRANCE, 11Service d’Oncologie Médicale, Hôpital Lyon Sud, Hospices Civils de Lyon, Lyon, FRANCE

Objectives: Principal: to assess the efficacy, determined by the proportion of patients who are free of progression, 6 months after starting talazoparib maintenance treatment (1 mg PO qd) after 4 to 6 cycles of platinum-based first line chemotherapy in patients with advanced malignant pleural and peritoneal mesothelioma.
Secondary: to assess other efficacy parameters and the safety; to identify predictive biomarkers of efficacy.

**Methods:** TALAMESO is an open-label, 3-independent-cohort phase II trial (Fleming’s single-stage) among patients with advanced malignant pleural (cohort A) or peritoneal (non-resected or incompletely resected disease (cohort B1) or with completely resected disease (cohort B2)) mesothelioma without any sign of disease progression after 4 to 6 cycles of platinum-based chemotherapy (including minimum 1 cycle of pemetrexed).

Primary endpoint is the proportion of patients free of progression 6 months after talazoparib start. Disease progression will be based on (i) tumor assessment according to the RECIST 1.1 criteria and mRECIST criteria and/or, (ii) CA125 high value (>34 U/mL will be considered elevated), (iii) death related to disease progression.

Secondary endpoints are PFS, OS, and safety (NCI-CTCAE v.5 criteria).

Deep molecular characterization will be performed at Lyon University Hospital on pre-treatment FFPE archived tumor tissue. Specifically, BAP1 protein expression and MSS/MSI status will be studied using IHC, BAP1 and HR genes will be sequenced and an innovative HRD transcriptomic signature using GeoMx Digital Space Profiling approach (Nanostring) will be evaluated and correlated with treatment response.

Key patient eligibility criteria: pathologically - or cytologically - proven malignant pleural or mesothelioma peritoneal mesotheliomas (epithelioid, sarcomatoid, biphasic), ECOG-PS ≤2, maximum 8 weeks interval between last chemotherapy cycle and talazoparib first administration (1 mg q.d)

In cohort A, pleura mesothelioma patients will have been treated by primary or interval debulking surgery with or without hyperthermic intrapleural or intrathoracic chemotherapy. In cohort B, peritoneal mesothelioma patients will had a primary or interval debulking surgery (B1: CC2-3 or B2: CC0-1) ± HIPEC.

In case of minimum 8/17, 7/14 and 7/9 observed successes respectively in cohort A, B1 and B2, the opportunity of randomized phase II or phase III will be discussed.

Durations of expected treatment period are 12 months in Cohort A, and 22 and 24 months for patients from Cohort B1 and B2, respectively.

Patients are followed until death or last documented patient encounter with a minimum of 1 year after end of treatment.

**Results:** The trial will be opened in Spring 2020. The study protocol will be complete, including instructions for electronic data management, imaging transfer and CT analysis, central pathology review and molecular pathology processing.

**Conclusion:** TALAMESO is the first phase II trial to evaluate efficacy and safety of PARPi talazoparib maintenance in malignant pleural and peritoneal mesothelioma. The study is supported by an independent research grant from Pfizer.

**Keywords:** Malignant mesothelioma, talazoparib, PARPi, BAP1, transcriptomic signature, maintenance treatment

---

**P047: Durvalumab with Chemotherapy as First Line Treatment in Advanced Pleural Mesothelioma - A Phase 3 Randomised Trial. The DREAM3R Trial**

**Nowak A**123, Forde P4, Kok P5, Brown C5, Sun Z6, O’Byrne K7, Yip S8, Anagnostou V9, Cook A23, Lesterhuis W2, Hughes B6, Johnson L10, Oostendorp M6, Marinucci D10, Fitzpatrick K10, Cummins M6, Pavlakis N11, Brahmer J4, Stockler M6, Ramalingam S4

1Sir Charles Gairdner Hospital, Australia, 2National Centre for Asbestos Related Diseases, University of Western Australia, Australia, 3Medical School, University of Western Australia, Australia, 4Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, USA, 5NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Australia, 6IBCSG Statistical Center, Boston, USA, 7Princess Alexandra Hospital and Queensland University of Technology, Australia, 8IBCSG Statistical Center, Boston, USA, 9Bloomberg-Kimmel Institute for Cancer Immunotherapy, John Hopkins, Baltimore, USA, 10The Prince Charles Hospital, Cancer Care Services, and University of Queensland, Australia, 11PrECOG, Philadelphia, USA, 12Northern Cancer Institute and University of Sydney, Australia, 13Winship Cancer

---
ABSTRACTS

Institute, Emory University Hospital, Atlanta, USA

Poster Session, Virtual, May 7, 2021

Objective: Standard first line treatment for unresectable malignant pleural mesothelioma (MPM) is platinum-based chemotherapy with pemetrexed. Two recent, single-arm, phase 2 trials (DREAM and PrE0505) combining the PD-L1 inhibitor durvalumab and standard first line cisplatin and pemetrexed (CP) exceeded pre-specified criteria for proceeding to phase 3. DREAM3R aims to determine the effectiveness of adding durvalumab to first line CP chemotherapy in advanced MPM.

Methods: Treatment naïve patients with advanced MPM will be randomised (2:1) to either durvalumab 1500 mg every 3 weeks, with doublet chemotherapy (cisplatin 75 mg/m2 and pemetrexed 500 mg/m2) every 3 weeks for 4-6 cycles, followed by durvalumab 1500 mg every 4 weeks until disease progression, unacceptable toxicity or patient withdrawal; or doublet chemotherapy alone for 4-6 cycles, followed by observation. The target sample size is 480 patients (320 durvalumab, 160 control) recruited over 27 months, with follow up for an additional 24 months. This provides over 85% power if the true hazard ratio for overall survival was 0.70, with 2-sided alpha of 0.05, and assuming a median survival of 15 months in the control group. Key inclusion criteria: MPM of all histologies, measurable disease per modified RECIST 1.1 (mRECIST 1.1) without prior radiotherapy to these sites, ECOG 0-1 and adequate bone marrow, kidney and liver function tests. Key exclusion criteria: prior systemic anticancer treatment or immunotherapy for MPM, diagnosis on cytology or fine needle aspiration biopsy only, contraindication to immunotherapy, and conditions requiring immunosuppressive or corticosteroids. Stratification: Age (18-70 years vs. > 70), gender, histology (epithelioid vs. non-epithelioid), and region (USA vs. ANZ). The primary endpoint is overall survival. Secondary endpoints include progression-free survival; objective tumour response (by mRECIST 1.1 and iRECIST); adverse events; health-related quality of life; and healthcare resource use. Tertiary correlative objectives are to explore and validate potential prognostic and/or predictive biomarkers (including features identified in the DREAM and PrE0505 studies, PD-L1 expression, tumour mutation burden and nuanced genomic characteristics, and HLA type) in tissue and serial blood samples. An imaging databank will be assembled for validation of radiological measures of response and studies of possible radiomic biomarkers in mesothelioma. ClinicalTrials.gov Identifier: NCT04334759 and ACTRN 12620001199909.

Immunotherapy, trial, durvalumab, mesothelioma, checkpoint inhibitor.

P048: Safety Outcomes of Intracavitary Cisplatin-fibrin Chemotherapy after Macroscopic Complete Resection for Malignant Pleural Mesothelioma: Insights from the Influencemeso Phase II Trial

Werner R1, Lauk O1, Kirschner M1, Meerang M1, Opitz I1

1University Hospital Zurich, Department Of Thoracic Surgery, Zurich, Switzerland

Poster Session, Virtual, May 7, 2021

Objectives: Intracavitary chemotherapy may be a promising additional modality to prevent early local recurrence after macroscopic complete resection (MCR) in malignant pleural mesothelioma (MPM). Until now, intracavitary therapy is not a standard therapy approach and has only been investigated in clinical trials. In our preclinical animal model and in a previous dose escalating clinical phase I trial, we investigated the intraoperative cisplatin-fibrin application after induction chemotherapy followed by macroscopic complete resection. The first results from this phase I trial showed promising pharmacokinetics with high local cisplatin dose levels and without systemic, dose-limiting toxicity. Following this dose-finding study, we performed a confirmation phase II clinical trial evaluating intracavitary cisplatin-fibrin application at a dose of 44mg/m2 body surface area (BSA). This abstract reports results from the safety assessment of the phase II INFLuenCe Meso trial.

Methods: Between November 2015 and August 2019, 20 patients (International Mesothelioma Interest Group Stage I-III) underwent extended pleurectomy and decortication (n=19) or partial pleurectomy (n=1) with the intent of MCR. Cisplatin-fibrin (44mg/m2 BSA) was sprayed on the resected surfaces of the chest wall and
the lung parenchyma. Adverse events (AEs) and serious adverse events (SAEs) were recorded until 56 days and 126 days (postoperative study visits) after cisplatin application, respectively. AEs and SAEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (06/2010) or 5.0 (11/2017). Hematologic and serologic parameters were assessed on postoperative days (POD) 0, 1, 2, 3, 4, 5, 7, 10 and 14, as well as on the first two postoperative visits.

**Results:** A total of 265 AEs were reported, among which 19 were categorized as SAEs. 30-day mortality was 0%. According to the CTCAE grading, 98 AEs (37.0%) were classified as grade I (mild), 93 AEs (35.1%) were classified as grade II (moderate), 70 AEs (26.4%) were classified as grade III (severe) and 4 AEs (1.5%) were classified as grade IV (life-threatening).

The most common SAE was postoperative pleural empyema, occurring in four patients. The therapy regimen consisted of repeated surgical debridement and vacuum assisted device (V.A.C.) changes. All four patients recovered without sequelae. Postoperative chylothorax was encountered in two patients and management of this SAE included total parenteral nutrition in both patients and additional operative ligation of the leak in one patient. Both patients fully recovered. In one patient, a hemothorax on the second postoperative day with subsequent circulatory arrest required cardiopulmonary resuscitation and emergent reoperation. He made a full recovery and was discharged 14 days after the study intervention.

**Conclusion:** In this first interim analysis we report a mortality rate of 0%. Among 20 patients undergoing intracavitary cisplatin-fibrin application for malignant pleural mesothelioma, 72.1% of all adverse events were classified as mild or moderate.

**P049: The Mesotrap Trial – The Challenges of Recruiting a High Morbidity Subgroup of Malignant Pleural Mesothelioma Patients to an Interventional Study**

Rintoul R1,2, Sharples L3, Freeman C2, Fox-Rushby J4, Tod A5, Maskell N6, Hughes V2, Rahman N7, Waller D8

1 University Of Cambridge, UK, Cambridge, United Kingdom, 2 Royal Papworth Hospital, Cambridge, United Kingdom, 3 London School of Hygiene and Tropical Medicine, London, United Kingdom, 4 King’s College London, London, United Kingdom, 5 University of Sheffield, Sheffield, United Kingdom, 6 University of Bristol, Bristol, United Kingdom, 7 University of Oxford, Oxford, United Kingdom, 8 St Bartholomew’s Hospital, London, United Kingdom

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Trapped lung in malignant pleural mesothelioma (MPM) occurs when the lung fails to fully re-inflate following pleural effusion drainage causing repetitive cycles of fluid re-accumulation, breathlessness and drainage. A challenging condition to manage with high morbidity and mortality, there is no consensus on the best way to manage it. Some offer insertion of an indwelling pleural catheter under local anaesthesia while others adopt video-assisted thoracoscopic partial pleurectomy/decortication to allow the lung to re-expand. The rationale for the MesoTRAP trial is to provide high-quality evidence for the optimal management of trapped lung in MPM patients in their final months of life.

**Methods:** MesoTRAP is a multi-centre open-label randomised controlled pilot and feasibility study comparing video-assisted thoracoscopic pleurectomy/decortication versus indwelling pleural catheter in patients with trapped lung and pleural effusion due to MPM. We are employing visual analogue scale (VAS) scores to measure dyspnoea and chest pain, assessing post-treatment complications, measuring resource and health service use and monitoring quality of life at 6 weeks, 3, 6 and 12 months post randomisation in each treatment group. If the pilot clinical trial is successful in recruiting and randomising 38 patients we will develop the trial into a phase III study.
ABSTRACTS

In order to capture data on patients who did not meet eligibility criteria for recruitment or who declined to participate, we have set up an observational sub-study. Patients in the sub-study will receive the same baseline and follow-up visits as those in the main study but will receive standard clinical care as directed by their clinician.

Results: To date, of 105 patients initially identified with trapped lung across 14 centres, 10 have been randomized, 6 to IPC and 4 to surgery. The main reason for not meeting eligibility criteria is that the clinical team thought the patient unfit for the surgical arm in 26 cases. Other reasons for not randomising include: declined participation (21 patients), patient survival estimated at <4 months (7 patients, of whom 3 died shortly after diagnosis), joined another clinical trial (5), no pleural effusion present (3), trapped lung resolved spontaneously (2). Sixteen remain in screening. Of the 21 patients who declined participation in the randomized study, 9 have participated in the observational sub-study.

Conclusion: MesoTRAP has proven to be a challenging study to recruit to mainly because of the co-morbidity of the patient group leading to a high screen failure rate. In addition to patients in the randomized trial the development of an observational sub-study has boosted recruitment and will allow us to capture valuable information around patient symptomatology, quality of life, resource and health service use in this challenging condition. Due to the pandemic, MesoTRAP has now closed and is in follow up. We aim to provide insights into how best to manage trapped lung in MPM.

https://clinicaltrials.gov/ct2/show/NCT03412357

The study is funded by the National Institute for Health Research for Patient Benefit PB-PG-1014-35050. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.


Sidhu C1,2, Lee G1,3,4

1Sir Charles Gairdner Hsopital, , Australia, 2Edith Cowan University, , Australia, 3University of Western Australia, , Australia, 4Institute of Respiratory Health, , Australia

Poster Session, Virtual, May 7, 2021

Objectives: Malignant pleural effusions (MPEs) are common but no consensus exists on the best definitive therapy for its control. Video-assisted thorascopic surgery (VATS) is often regarded as the most effective therapy in patients fit for surgery. Recent randomized controlled trials (RCTs) suggest that ambulatory drainage with indwelling pleural catheters (IPC) can improve symptoms and quality-of-life, while minimizing the need of hospitalization and further pleural interventions. AMPLE (Australasian Malignant Pleural Effusion)-3 is a multicentre RCT designed to address this equipoise.

Methods: Patients with symptomatic MPEs are randomized 1:1 to IPC (+talc slurry) or VATS pleurodesis. Key inclusion criteria are a predicted survival of ≥6 months; ECOG performance status 0 or 1. Exclusion criteria include age <18 years, American Society of Anaesthesia score >3, suspected pleural infection, significant pleural fluid loculations, chylothorax, uncorrectable bleeding diathesis and previous ipsilateral lobectomy/pneumonectomy. The primary endpoint is the percentage of patients in each arm requiring repeat invasive pleural interventions for symptomatic effusion recurrence within 12 months. Secondary endpoints include time to effusion recurrence, overall survival, days in hospital, analyses of symptoms/quality of life (QoL) measures, adverse events and economic analyses. The study aims to recruit 158 participants, which includes an anticipated 5% drop-out rate. Participants will be reviewed 7-10 days post-procedure, monthly for 6 months, then at 9 months and 12 months post-procedure. Data collected include patient characteristics (including malignancy history and treatments), IPC and VATS procedural aspects,
radiological data (chest x-ray and ultrasounds), adverse events and symptom/QoL questionnaires.

**Results:** The study first commenced recruitment in late 2019 at the primary site (Sir Charles Gairdner Hospital, Western Australia). 13 additional sites have become involved in Australia (Hollywood Hospital, St John of God Hospital – Midland, Fiona Stanley Hospital, St John of God Hospital – Murdoch, Royal Adelaide Hospital, Northern Hospital, Sunshine Coast Hospital, Prince Charles Hospital, Concord Hospital, St Vincent's Hospital, Sutherland & St George Hospital), New Zealand (Wellington Hospital) and Canada (Toronto General Hospital). 33 patients have been recruited to date (January 2021).

**Conclusion:** This study will inform about the optimal management of MPE in patients who have a reasonable life expectancy and are fit for surgery. Centres/investigators interested in participating in the trial can contact the study coordinators.

Study coordinators contact: Calvinjit.Sidhu@health.wa.gov.au, Ai.Tan2@health.wa.gov.au

Mesothelioma, Pleural Effusions, Pleural, Indwelling pleural catheter, Video-assisted thorascopic surgery

---

**P052: EORTC 1205: Randomized Phase 2 Study of Pleurectomy/Decortication (P/D) Preceded or Followed by Chemotherapy in Patients (pts) with Resectable Malignant Pleural Mesothelioma (MPM)**


1Antwerp University Hospital, Edegem, Belgium, 2Ghent University Hospital, Ghent, Belgium, 3National cancer Institute, Cairo, Egypt, 4Erasmus MC, Rotterdam, Netherlands, 5EORTC data center, Brussels, Belgium, 6Netherlands Cancer Institute, Amsterdam, the Netherlands

**Poster Session, Virtual, May 7, 2021**

**Objectives:** P/D is considered a valid and less morbid alternative surgical approach for extrapleural pneumonectomy in selected patients with resectable MPM. The procedure however, is poorly standardized and never radical. Therefore it is preferably preceded or followed by systemic chemotherapy.

Aim: EORTC 1205 aims at comparing the feasibility and optimal sequencing of chemotherapy with P/D with regard to overall treatment time and feasibility.

**Methods:** Functionally operable treatment-naïve patients with T1-3 N0-2 epithelial or biphasic mesothelioma and PS 0-1 are randomized between adjuvant (arm A) and neo-adjuvant chemotherapy (arm B). Chemotherapy in both arms consists of 3 cycles of cisplatin and pemetrexed at standard dosage and premedication. P/D is performed by experienced thoracic surgeons in credentialed centers. Strict timelines between both procedures apply and surgical quality is audited with intra-operative mapping and imaging and comprehensive registration of complications. Primary endpoint in the intention-to-treat population is successful completion of the multimodality treatment within 20 weeks and being alive with no signs of PD or persistent grade III-IV toxicity.

**Results:** As of October 16, 2019, 37 patients of the required sample size of 64 have been randomized and 26 underwent surgery. Baseline patient and tumor
characteristics appear well balanced so far (table 1).

**Conclusion:** trial accrual proceeds on schedule with the last patient expected to be enrolled in 2020. A protocol amendment allows carboplatin/pemetrexed as induction regimen. An updated analysis will be presented at the IMIG meeting.

**Keywords:** mesothelioma, pemetrexed, pleurectomy, decortication, surgery, chemotherapy
**P053: The Western Australia Mesothelioma Registry – Update**

**Brims F**, Franklin P, Olsen N, Segal A, Sodhi-Berry N, de Klerk N, Alsion R, Musk B

1Curtin Medical School, Perth, Australia, 2Sir Charles Gairdner Hospital, Perth, Australia, 3University of Western Australia, Perth, Australia, 4PathWest Laboratories, Perth, Australia, 5Curtin University, Perth, Australia

**Poster Session, Virtual, May 7, 2021**

**Objectives:** The Western Australia Mesothelioma Registry (WAMR) has been collecting data on every case of malignant mesothelioma (MM) in WA since 1960. The aim of this study was to report the main findings from the WAMR.

**Methods:** Potential cases are notified through the WA Cancer Registry. Every case is confirmed by an expert pathologist and each case has the most significant source of asbestos exposure and year of first exposure recorded. Six ‘exposure’ classifications were used: first wave exposures (working with raw asbestos), second-wave exposures (working with manufactured asbestos products), non-occupational third-wave exposures (DIY), other non-occupational exposures (eg Wittenoom residents, family members of asbestos workers), unknown exposure and no-known exposure. Both the number of cases and age-standardised incidence rates (ASIRs) were calculated for males and females for 5-year periods from 1980 (when the first DIY case was observed) to September 2019.

**Results:** Between 1980 and 2019, there were 2724 cases (2356 male) of MM in WA. Of these, 216 (8.3%) cases (125 male) were classified as DIY exposures. DIY accounted for nearly 22% of female cases and 5.4% of male cases. Incidence rates for DIY MM increased from 0.4/1,000,000 in 1980/84 to over 13.5/1000000 in 2005/09. However, ASIRs decreased slightly in 2010/14 (11.4/1000000) and 2015/19 (9.9/1000000). Only 3 DIY cases were ‘exposed’ after the ban on amphibole asbestos in building materials in the mid-1980s. Pleural MM accounted for 2551 (93.7%) of cases, 1677 (61.6%) of cases were epithelioid MM. Latency between first exposure and diagnosis has increased significantly since over time (Table 1, p<0.0001)

**Conclusion:** In WA, MM from DIY is a more common exposure in females than males. Latency time is increasing. WA is yet to reach a plateau in cases of MM.

**Keywords:** epidemiology

---

**Table 1. WAMR data of latency from 1st exposure to diagnosis of MM, stratified by decade.**

<table>
<thead>
<tr>
<th>Decade</th>
<th>n</th>
<th>Median (yrs)</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre 1980</td>
<td>84</td>
<td>28</td>
<td>22-40</td>
</tr>
<tr>
<td>1981-1990</td>
<td>287</td>
<td>37</td>
<td>29-53</td>
</tr>
<tr>
<td>1991-2000</td>
<td>590</td>
<td>45</td>
<td>36-56</td>
</tr>
<tr>
<td>2001-2010</td>
<td>868</td>
<td>50</td>
<td>42-60</td>
</tr>
<tr>
<td>Post 2010</td>
<td>892</td>
<td>56</td>
<td>47-68</td>
</tr>
<tr>
<td>IQR = Interquartile Range</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
P054: Oxidative Stress and Inflammation in Automobile Mechanics Handling Asbestos Rich Vehicle Parts

Dhakal N1, Bhandari S1, Gautam B1, Shrestha S1

1Gandaki Medical College, Pokhara, Nepal

Poster Session, Virtual, May 7, 2021

Objectives: Oxidative stress and inflammation are speculated to be an important part of asbestos related malignant and non-malignant pulmonary pathology, however, the results are not conclusive. Despite of widespread use of asbestos containing material, studies pertaining to asbestos exposure and its effects are negligible from our setting, which warrants the need of this study.

We aimed to determine high sensitive-CRP (hs-CRP), Total antioxidant capacity (TAC), Total peroxides (TP) and plasma Malondialdehyde (pMDA) and compare between cases with asbestos exposure and healthy controls.

Methods: A total of 52 cases of automobile mechanics working in brake and clutch repairing workshop and 58 matched healthy controls were recruited for the study. General anthropometric and biochemical parameters were measured in both groups and compared. Those with known case of any chronic disease, under medication, those with acute or seasonal disease and those unwilling to participate were excluded. The statistical analysis was done with p value <0.05 as statistically significant.

Results: The average duration of occupation for cases was about 9 years. Cases with asbestos exposure had higher level of pMDA, TP and hs-CRP with reduced level of TAC as compared to healthy controls (p<0.001). Furthermore, it was found that the level of pMDA, TP and hs-CRP increased whereas TAC declined as the duration of exposure expanded (p<0.001). Likewise, the level of pMDA, TP and hs-CRP was higher while the level of TAC was lower in cases than in controls independent of tobacco consumption (p<0.001).

Conclusion: Asbestos exposure is accompanied by inflammation and oxidative stress. Thus, early management of these derangements could be clinically valuable to prevent asbestos related pathology.

Keywords: Asbestos, oxidative stress, inflammation

P055: Gendered Experiences of Asbestos Exposure, Mesothelioma Risk and Pursuing a Civil Compensation Claim

Ejegi-Memeh S1, Robertson S1, Ejegi-Memeh S2, Darlison L2

1Division of Nursing and Midwifery, University of Sheffield, Sheffield, United Kingdom, 2Respiratory Medicine, University Hospitals of Leicester, Leicester, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: There is increasing concern from health and other professionals (including asbestos support advisors and lawyers) that women with mesothelioma are less likely to be aware of the nature of their asbestos exposure and workplace risk. Additionally, there is a suggestion that women are more likely to encounter assumptions that they were exposed through para-occupation e.g. from work clothes of male family member rather than their own occupational or environmental exposure. To date these concerns have been based on anecdote, expert opinion or incomplete data sets.

This paper presents early qualitative findings from a larger mixed-methods study, the Gendered Experiences of Mesothelioma Study (GEMS). GEMS is a Mesothelioma UK collaborative study that is being conducted by the Mesothelioma Patient Experience Research Group, University of Sheffield. The aim of GEMS is to examine the experiences of the mesothelioma patient journey from exposure, through to symptom presentation, diagnosis, treatment and supportive care. Specifically, this paper considers the gendered experience of asbestos exposure, mesothelioma risk and pursuing a civil claim.

Methods: This UK qualitative health services research study involved semi-structured interviews with 9 women and 5 men with mesothelioma. Recruitment was conducted via trusted charitable organisations including Mesothelioma UK and Asbestos Support Groups in the UK. Interviews were transcribed, anonymised and analysed using Thematic Analysis techniques.

Results: The findings provide unique insight into the gendered experience of asbestos exposure, mesothelioma risk and pursuing a civil claim. The relationship between men and women’s responses to a diagnosis
of mesothelioma is also considered. There appears to be a lack of awareness of asbestos risk outside of the traditional occupations. Thus there was a perception that mesothelioma is a male and older person’s disease. This lack of perception led to a sense of disbelief when women, and particularly, younger women, were diagnosed.

Participants’ experiences indicated that there are assumptions made by health and legal professionals that women’s asbestos exposure would be para-occupational. Examples were provided where women initially identified para-occupational exposure through a male family member’s work but then later went on to identify primary exposure from their own work. When this was the case, it was then too late to claim.

Gendered differences were found to influence whether a civil claim was pursued. In cases of para-occupational exposure, wanting to preserve the feelings of the male family member was a factor that some women took into consideration. In some cases, women also did not pursue claims as they presumed it would be unsuccessful. In comparison, men, particularly those responsible for the financial well-being of the family, wanted to ensure that their wives were financially stable in the event of their deaths.

**Conclusion:** The findings indicate that awareness and understanding of asbestos exposure are influenced by gender. Participants’ descriptions provided insight into factors that influence decisions regarding pursuing civil compensation claims. This may be a deterrent to women making a civil compensation claim. The findings have implications for how occupational, workplace and environmental risk is discussed with men and women receiving a diagnosis of mesothelioma.

**Keywords:** Mesothelioma, gender, asbestos exposure, mesothelioma risk, civil compensation claims

**P056: An Audit to Explore the Demographics of Patients Diagnosed Within Kent**

**Gilham L**

1*Mesothelioma UK, United Kingdom, 2Kent Oncology Centre, United Kingdom*

**Poster Session, Virtual, May 7, 2021**

**Objectives:** In the UK around 2,700 people are diagnosed with mesothelioma each year. Over 120 cases of mesothelioma are diagnosed each year within Kent. An audit was undertaken by Louise Gilham, Mesothelioma UK Nurse, to explore the demographics of patients diagnosed with Mesothelioma within Kent.

**Methods:** An audit was undertaken in real time over a 10 month period. The Lung CNS teams from four NHS Trusts across Kent provided the Mesothelioma UK Nurse with the patients’ demographics to include gender, age, occupational history and exposure to asbestos. The occupational history was then cross referenced with information provided by the Asbestos Support Groups – LASAG and HASAG.

**Results:** Demographics from 98 patients diagnosed with mesothelioma were reviewed. Data from all four NHS Trusts showed similar trends with: age (Median Age 76). Mesothelioma histological sub-types: (Epithelioid 59%, sarcomatoid 8%, Biphasic 11%, Radiological diagnosis 12%, unspecified 9%, testicular unspecified 1%). Gender: Male to Female ratio 83:15.

The occupation and asbestos exposure of all 98 patients were grouped into 10 categories these being Manual Trades, Car industry, Office / Admin, Factory workers, Public Sector, Power stations, MOD / dockyards, Secondary exposure, Miscellaneous and Unknown exposure.

**Conclusion:** Asbestos exposure through manual trades had the highest percentage at 47%, and Dockyard / MOD 9%. Kent traditionally had a high incidence of mesothelioma due to close proximity to Chatham and the London Docks but this data suggests that only 9% were exposed there. This data supports the gradual change in the occupational exposure trends we are now seeing, moving away from the traditional dockyard / MOD workers to the manual trades, DIY and public sector workers.

**Keywords:** demographics, Occupation / Exposure
**P057: Does the Number of Patients with Mesothelioma Reported Through the Cancer Data Set Correlate with the Number of Patients Diagnosed Within Kent?**

*Gilham L*\(^1\)

\(^1\)Mesothelioma UK, Leicester, United Kingdom, \(^2\)Kent Oncology Centre, United Kingdom

**Poster Session, Virtual, May 7, 2021**

**Objectives:** The UK has the highest incidence of mesothelioma in the world. The county of Kent in the South East of the UK has a high incidence of mesothelioma due to the close proximity of both Chatham and the London Docks. On average 120 patients per year are diagnosed in Kent across four NHS Trusts.

In 2017 Louise Gilham took up the post of Mesothelioma UK Nurse for Kent. This role enabled Louise to undertake an audit over a 10 month period to explore if: “The number of patients with mesothelioma reported through the Cancer Data Set correlate with the number of patients diagnosed within Kent?”

**Methods:**

Data collection

Patient data to include: NHS number and histological subtype was collected from Lung CNS’s, MDM Coordinators, HCP’s and two Asbestos Support Groups - LASAG / HASAG. This data was collated and analysed from each of the four NHS Trusts with each Trust having a separate Excel sheet. Data was then extracted from the Cancer Data Set using the ICD code of C45 Malignant Mesothelioma and SNOMED Codes 90503, 90513, 90523, 90533.

Cross reference comparison using the NHS number was then conducted.

**Results:**

Comparative Analysis

91 patients details had been provided to the Mesothelioma UK Nurse

51 patients had been coded correctly on the Cancer Data Set using a ICD Code C:45

51 / 91 = 56% coded correctly.

**Conclusion:**

Implications / Recommendations for future practice

This audit suggests that the number of patients with mesothelioma reported through the Cancer Data Set does not correlate with the number of patients diagnosed within Kent.

Implications for clinical practice include:

- Local and National statistics will be inaccurate and unreliable.
- Workforce planning and resource allocation will be underestimated and underfunded.
- The need for post mortem without documented histology / coding will be greater.

**Keywords:** ICD Diagnosis codes

---

**P058: Burden of Asbestos Related Diseases in Taiwan Based on Taiwan Cancer Registry and National Health Insurance databases**

Chen C\(^1,2\), Cheng Y\(^3\), **Lee L**\(^{1,2,4,5,6}\)

\(^1\)Department of Environmental and Occupational Medicine, National Taiwan University Hospital, Taipei, Taiwan, \(^2\)Institute of Environmental and Occupational Health Sciences, National Taiwan University, Taipei, Taiwan, \(^3\)Institute of Health Policy and Management, National Taiwan University, Taipei, Taiwan, \(^4\)National Institute of Environmental Health Sciences, National Health Research Institutes, Miaoli, Taiwan, \(^5\)Departments of Neurology and Stroke Center, National Taiwan University Hospital, Taipei, Taiwan, \(^6\)Research Center for Environmental Medicine, Ph.D. Program of Environmental and Occupational Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

**Poster Session, Virtual, May 7, 2021**
Objectives: Occupational and environmental exposure to asbestos is a crucial risk factor for asbestos-related diseases (ARDs), including malignant mesothelioma (MM), lung cancer, laryngeal cancer, ovarian cancer, and asbestosis. Because of the relatively long latency period of ARDs, and a general lack of public awareness, there are barriers and difficulties in recognition, and their underestimation could be a public health challenge. Few studies analyzed the trend of ARDs or evaluated their extent of under-estimation in Taiwan. This study aimed to estimate the disease burden of ARDs during 2005-2017 and to evaluate magnitude of their under-estimation.

Methods: Incident cancer cases were retrieved from the Taiwan Cancer Registry (TCR) for MM, lung cancer, laryngeal cancer, ovarian cancer, pharyngeal cancer, gastric cancer, and colorectal cancer from 2005 to 2017. Incident cases of asbestosis were based on the National Health Insurance (NHI) databases, available in 2005, 2010, and 2015, and compared with data of workers’ compensation. The cases of ARDs attributable to asbestos were estimated using population attributable fraction (PAF). The prevalence of asbestos exposure was estimated through retrospective exposure assessment using worker population in various industries, and CARcinogen EXposure (CAREX). Relative risks of the ARDs of interest were drawn from epidemiological literature searched in the PubMed database.

Results: PAF of MM and asbestosis was assumed to be 100%, and PAF of the other ARDs ranged from 0.14% (colorectal cancer) to 2.31% (lung cancer) in 2015. Estimated incident case numbers of asbestos-related malignancies were summarized in Table 1. There were only less than three incident cases of asbestosis in 2005 and 2010, and there were five male cases and less than three female cases in 2015.

Conclusion: ARDs would impose a substantial burden on Taiwanese workers in that about 400 cancer cases annually may be attributable to occupational asbestos exposure. We observed obvious underestimation of ARDs in comparison with real-world statistics of worker’s compensation. Collaborative efforts to increase awareness of work-related ARDs in the general public and among clinicians are urgently needed. Appropriate health exam programs with cancer screening should be designed considering cost-effectiveness for workers even after retirement for early detection of ARDs.
P059: Prognostic Factors in Malignant Pleural Mesothelioma. Validation of the CALGB and EORTC Prognostic Systems

Madrzak J1, Jaskiewicz P2, Bryl M3, Sinacki M1, Kowalski D2, Spychalski L3, Krzakowski M2, Ramlau R4, Dzidziszko R1, Jassem J1

1Department of Oncology and Radiotherapy, Medical University of Gdansk, , Poland, 2Department of Thoracic Malignancies, Maria Sklodowska-Curie National Institute of Oncology in Warsaw, , Poland, 3Department of Clinical Oncology, Great Polish Centre of Pulmonology and Thoracic Surgery in Poznan, , Poland, 4Department of Oncology, Poznan University of Medical Sciences, Poland

Poster Session, Virtual, May 7, 2021

Objectives: Malignant pleural mesothelioma (MPM) is as a rare malignancy with increasing incidence. Despite recent progress in diagnostics and combined treatment, prognosis in MPM is grim and most patients succumb to their disease. The aim of this study was to analyze selected clinical prognostic factors in a large series of MPM patients treated in three tertiary Polish institutions, and to validate clinical utility of prognostic systems proposed by CALGB and EORTC.

Methods: Study group included 218 MPM patients treated between 1999 and 2012. All but one patients (99.5%) received primary chemotherapy using various regimens. Further treatment was individualized and included subsequent chemotherapy, radiotherapy or occasionally surgery. Complete and partial remission after primary chemotherapy was achieved in 2 (1%) and 42 (19%) patients, respectively; 119 patients (55%) had stable and 53 (24%) progressive disease. Second and third-line chemotherapy, and palliative radiotherapy were used in 52%, 12% and 18% of patients, respectively. The impact of selected demographic and clinical variables on overall survival was evaluated in univariate and multivariate analyses. All patients were assigned to appropriate low or high risk groups of the EORTC prognostic system, and to 6 prognostic groups according to the CALGB system.

Results: The median survival in the entire study group was 12.6 months. One-year and two-year survival rates were 52% and 21%, respectively. In the univariate analysis older age, worse performance status, presence of pain, longer symptom duration, thrombocytosis, high level of LDH, leukocytosis and higher tumor stage were significantly related to shorter survival. Of those, worse performance status, presence of pain, high level of LDH, leukocytosis and higher tumor stage were significant in the multivariate analysis. Both EORTC and CALGB prognostic systems properly identified particular prognostic groups. However, in multivariate models assessing interactions among particular variables, the CALGB system appeared to better differentiate survival (using Broadside and Tackle software, the p-values for the CALGB and EORTC classifiers were 6.35E-07 and p=4.53E-04, respectively). The best discrimination values were obtained by grouping 6 CALGB groups into 3 categories (1+2, 3+4 and 5+6).

Conclusion: Both EORTC and CALGB prognostic systems were validated in our cohort. A modified version of the CALGB system was proposed. This simplified system could serve for stratification of patients in clinical studies and may facilitate treatment decisions in routine management of MPM patients.

P060: Mesothelioma Outcomes in Manitoba 2001 – 2015

Maksymiuk A1, Kudlovich R2, Lambert P1, Wawryko P2

1CancerCare Manitoba, Winnipeg, Canada, 2University of Manitoba, Winnipeg, Canada

Poster Session, Virtual, May 7, 2021

Objectives: Review of outcomes (response, survival) of all patients in our jurisdiction with biopsy-confirmed mesothelioma diagnosed between 2001 and 2015 to assess the impact of changes in therapy during this interval of time and characterize clinical correlates of outcome (survival).

Methods: All patients with mesothelioma are registered with the provincial cancer registry. The 2015 cut-off was selected to ensure adequacy of follow-up for all studied patients. Cases were divided into three 5-year cohorts for comparison: Cohort 1 2001-2005, Cohort 2 2006-2010, Cohort 3 2011-2015. Data were obtained from the medical records, tabulated and analyzed to compare clinical features, response to therapy and survival.
**Results:** In total, 275 cases of mesothelioma were diagnosed within this 15 year time interval. There were no differences between cohorts in median age, gender, histologic sub-type or location of primary mesothelioma. The median survival for the entire group was 8 months (<1 – 144 mos). For 150 patients who were not treated, median survival was 3 months from diagnosis. For 125 patients who were treated with systemic therapy, median survival was 14 mos for cohort 1, 13 mos for cohort 2 and 16 mos for cohort 3 respectively. Two BAP-1 germline mutation-positive familial clusters were identified; one has previously unreported c.606G>T + c.1393A>G variant. Some correlates of survival > 48 mos are BAP-1 mutations, intraperitoneal disease treated with HIPEC intra-abdominal chemotherapy, young age and tunica vaginals primary site.

**Age (median, range):** 73 (27-95)

**Gender:** 223M (83%), 52F (17%)

**Pleural:** 240 (87%)

**Peritoneal:** 33 (12%)

**Other (testicular):** 2 (1%)

**Histology:** epithelial 36%, sarcomatoid 11%, mixed 12%, NOS 40%

**Survival, range (mos):** 8 (<1 – 144)

**Current survivors (mos):** 5 (48+, 48+, 60+, 72+, 78+)

**Conclusion:** Changes in therapy – mainly transitioning from cis/carboplatin + gemcitabine to cis/carboplatin + pemetrexed as 1st-line therapy in 2015 – appears to have resulted in marginal “real world” benefit in terms of improving outcomes. The availability of pemetrexed as a 2nd-line therapy was a factor in Cohort 1. Limited benefit was demonstrated for 2nd-line systemic therapy in Cohorts 2 and 3 or attempted surgical intervention.

**Keywords:** database outcome analysis

---

**P061: Outcomes from Palliative Chemotherapy for Malignant Pleural Mesothelioma: The Impact of Platinum-pemetrexed**

*Nasser A, Baird A, Saint-Pierre M, Laurie S, Wheatley-Price P*

1The Ottawa Hospital/University of Ottawa, Ottawa, Canada, 2Montfort Hospital/Division of Respirology, University of Ottawa, Ottawa, Canada

**Poster Session, Virtual, May 7, 2021**

**Objectives:** The preferred first-line chemotherapy regimen for malignant pleural mesothelioma (MPM) is pemetrexed plus cisplatin based on the pivotal 2003 phase III EMPHACIS trial. Pemetrexed was approved in Canada on May 21st, 2004. We aimed to investigate if there was an improvement in survival in our center after the introduction of pemetrexed in Canada.

**Methods:** With ethics approval, we collected and analyzed demographics, treatment and survival data on all patients with MPM treated in an academic cancer center between January 1991 and March 2019.

**Results:** In total 336 patients were included in the study, of whom 192 received chemotherapy. Demographic and survival data are summarized in table 1. Overall, 283 (84.2%) were men, 201 (59.8%) had epithelioid histology, and 204 (60.7%) had a good ECOG PS 0-1 at diagnosis. Patients in the later era were older (median age 74 vs 66 years) and less likely to have ECOG PS 0-2 (77% vs 89%). 70 patients (50%) in the earlier era (January 1991 – April 2004) received chemotherapy vs 117 (59.7%) in the later era (May 2004 – March 2019). The most common first-line therapy in the early era was cisplatin/doxorubicin +/- tamoxifen, received by nearly half the patients (45.7%), many of whom were enrolled in a clinical trial. After pemetrexed approval, the most common regimen was cisplatin/pemetrexed (53%) with a further 22% receiving carboplatin-pemetrexed.

Among the entire cohort (treated and untreated patients), median OS was not significantly different between the earlier and later time periods (9.26 versus 9.95 months, p=0.9). For patients who received chemotherapy, the median OS before and after the approval of pemetrexed
was 13.7 months and 13.2 months (p=0.29), respectively. However, when controlling for age, stage, performance status, sex, EPP, histology and other prognostic variables, we found a statistically significant improvement in OS with the pemetrexed-containing chemotherapy versus non-pemetrexed chemotherapy (HR: 0.59; 95% CI, 0.40-0.87; p=0.007)

**Conclusion:** Over the past three decades we observed a modest increase in the uptake of palliative chemotherapy and a small improvement in OS despite an increasingly older patient population.

<table>
<thead>
<tr>
<th></th>
<th>Pre-approval</th>
<th>Post-approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>140</td>
<td>196</td>
</tr>
<tr>
<td><strong>Gender (M/F)</strong></td>
<td>122/18</td>
<td>161/35</td>
</tr>
<tr>
<td><strong>Median age at diagnosis</strong></td>
<td>66.2</td>
<td>74.3</td>
</tr>
<tr>
<td><strong>Chemotherapy (%)</strong></td>
<td>70 (50.0)</td>
<td>117 (59.7)</td>
</tr>
<tr>
<td><strong>EPP (%)</strong></td>
<td>11 (7.90)</td>
<td>11 (5.61)</td>
</tr>
<tr>
<td><strong>ECOG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 (%)</td>
<td>92 (65.7)</td>
<td>112 (57.1)</td>
</tr>
<tr>
<td>2 (%)</td>
<td>31 (22.1)</td>
<td>40 (20.4)</td>
</tr>
<tr>
<td>3-4 (%)</td>
<td>15 (10.7)</td>
<td>26 (13.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1.43)</td>
<td>18 (9.18)</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most common (%)</td>
<td>Cisplatin, doxorubicin +/- tamoxifen (45.7%)</td>
<td>Cisplatin, Pemetrexed (53%)</td>
</tr>
<tr>
<td>Second most common (%)</td>
<td>Gemcitabine (21.4%)</td>
<td>Carboplatin, Pemetrexed (22%)</td>
</tr>
<tr>
<td>Third most common (%)</td>
<td>Cisplatin + Gemcitabine (17.1%)</td>
<td>Trial medications (12.8%)</td>
</tr>
<tr>
<td><strong>Median OS, months</strong></td>
<td>9.26</td>
<td>9.95</td>
</tr>
<tr>
<td><strong>Median OS chemo, months</strong></td>
<td>13.7</td>
<td>13.2</td>
</tr>
<tr>
<td><strong>Median OS no chemo, months</strong></td>
<td>4.37</td>
<td>4.44</td>
</tr>
</tbody>
</table>
**P062: Epithelioid Subtype Is the Most Significant Independent Favorable Prognostic Factor for Malignant Pleural Mesothelioma: A Real-world Danish Cohort**

Panou VL, Ringgaard T, Weinreich U, Meristoudis C, Røe O

1Odense University Hospital, Odense, Denmark, 2Aalborg University, Aalborg, Denmark, 3Levanger Hospital, Levanger, Norway, 4Department of Cancer Research and Molecular Medicine Norwegian University of Science and Technology (NTNU), Trondheim, Norway, 5Aalborg University Hospital, Aalborg, Denmark

**Poster Session, Virtual, May 7, 2021**

**Objectives:** The primary aim of this study was to investigate patient- and disease characteristics that are associated with survival in malignant pleural mesothelioma (MPM).

**Methods:** MPM cases diagnosed in Aalborg University Hospital in the North Denmark Region during 1972-2015 were re-evaluated by two expert pathologists using modern immunohistochemical techniques to verify the diagnosis. Information about the patients’ age at diagnosis, gender, survival, asbestos exposure, performance status (PS), significant comorbidities, type of treatment, MPM subtype and stage were gathered from the individual’s medical records and from the nationwide Danish registries. Fisher’s exact test, univariate and multivariate cox regression, Kaplan Meier estimate and log rank test was used for the statistical analyses. Variables with p<0.05 were considered significant.

**Results:** The study included 95 MPM patients that only received best supportive care (BSC group) and 184 that were treated with chemotherapy only or in combination with surgery and/or radiation (Treated group) (Table 1a). The Treated group consisted of more men (p=0.003), patients with heavier asbestos exposure (p=0.0004), better PS (p<0.00001), younger age (p<0.00001) and earlier MPM stage (p=0.002) (Table 1a). For the BSC group, significant favorable prognostic factors comprised good PS, female gender and epithelioid subtype (Table 1b). Only epithelioid subtype correlated significantly with better OS for the treated group (Table 1b, Figure 1).

**Conclusion:** In chemotherapy naïve MPM patients, independent positive prognostic factors are, by descending significance, epithelioid subtype, good PS and gender. In treated patients, epithelioid subtype is the only significant independent favorable prognostic factor for MPM. Studies on prognostic factors for both treated and untreated MPM patients are rare. The findings of the present study indicate that prognostic factors for patients that receive treatment and BSC may differ, while histology is a more prominent factor than age and PS in order to assess a patient’s eligibility for chemotherapy.
Table 1a. Displays the characteristics of the study population, divided into two categories depending on whether the patients received any kind of treatment or best supportive care.

Table 1b. Displays the univariate and multivariate Cox regression analysis for the baseline characteristics. Only variables with p < 0.05 in the univariate analysis were included in the multivariate regression analysis.

SD: Standard deviation.
IQR: Inter quartile range
TNM: Tumor Nodule Metastasis
HR: hazard ratio
CI: confidence interval
*Compared to no asbestos exposure

<table>
<thead>
<tr>
<th>Table 1a.</th>
<th>BSC group, N=25 (100%)</th>
<th>Treated group, N=124 (100%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>74.18 (8.9)</td>
<td>65.75 (8.6)</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Survival months, median (IQR)</td>
<td>4.0 (7.0)</td>
<td>17.0 (14.75)</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Gender, male, N (%)</td>
<td>66 (69.5)</td>
<td>157 (85.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Asbestos exposure N (%)</td>
<td>Occupational</td>
<td>52 (62.2)</td>
<td>161 (79.2)</td>
</tr>
<tr>
<td>Non-occupational</td>
<td>29 (31.7)</td>
<td>40 (18.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>None</td>
<td>14 (15.3)</td>
<td>7 (3.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>PS N (%)</td>
<td>Good</td>
<td>0</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>1</td>
<td>31 (32.6)</td>
<td>92 (50.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22 (23.2)</td>
<td>16 (8.7)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>21 (22.1)</td>
<td>3 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>17 (17.9)</td>
<td>0</td>
<td>0.21</td>
</tr>
<tr>
<td>Comorbidities, yes, N (%)</td>
<td>Epithelioid</td>
<td>61 (64.2)</td>
<td>105 (71.1)</td>
</tr>
<tr>
<td>Non-epithelioid</td>
<td>16 (16.8)</td>
<td>67 (36.4)</td>
<td></td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>18 (18.9)</td>
<td>12 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Stage N (%)</td>
<td>Early</td>
<td>TNM I</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>TNM II</td>
<td>13 (13.7)</td>
<td>41 (22.3)</td>
<td></td>
</tr>
<tr>
<td>TNM III</td>
<td>18 (18.9)</td>
<td>65 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>13 (13.7)</td>
<td>7 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Regional spread</td>
<td>13 (13.7)</td>
<td>14 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Late</td>
<td>TNM IV</td>
<td>32 (33.7)</td>
<td>35 (19.0)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>3 (3.2)</td>
<td>0</td>
<td>0.002</td>
</tr>
<tr>
<td>Treatment N (%)</td>
<td>Chemotherapy</td>
<td>0</td>
<td>94 (51.1)</td>
</tr>
<tr>
<td>Chemotherapy + Radiation</td>
<td>0</td>
<td>46 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy + Surgery</td>
<td>0</td>
<td>20 (10.9)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy + Radiation + Surgery</td>
<td>0</td>
<td>24 (13.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 1b.</th>
<th>BSC group</th>
<th>Treated group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td>Multivariate</td>
<td>Univariate</td>
</tr>
<tr>
<td>HR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.99</td>
<td>0.97-1.02</td>
</tr>
<tr>
<td>Gender, male</td>
<td>1.64</td>
<td>1.04-2.58</td>
</tr>
<tr>
<td>Occupational exposure*</td>
<td>1.05</td>
<td>0.58-1.90</td>
</tr>
<tr>
<td>Non-occupational exposure*</td>
<td>0.81</td>
<td>0.43-1.55</td>
</tr>
<tr>
<td>Subtype, epithelioid</td>
<td>0.52</td>
<td>0.34-0.81</td>
</tr>
</tbody>
</table>

*Compared to no asbestos exposure
P063: Human Ecology Associated with Asbestos-Related Diseases in Bangladesh

Rahman M¹

¹Freelance Public Health Consultant, Mymensingh, Bangladesh

Poster Session, Virtual, May 7, 2021

Objectives: Bangladesh is the largest ship-recycling country that has devastating impact on the marine and coastal resources including human health due to hazardous asbestos. There are other sources of hazardous asbestos in the country too. The study aims to delve into the situation of human health ecology (i.e., interlocking among population, organization, environment and technology) associated with asbestos in Bangladesh to suggest few mitigation measures.

Methods: Using Google Scholar search engine, web-based electronic recorded communication was consulted to find association of human ecology with asbestos-related diseases in Bangladesh for conceptual analysis and etic interpretation.

Results: An estimated 22,000 workers in Bangladesh’s ship-breaking industry are exposed to precariously elevated levels of asbestos. More than 35 percent of the ship-breaking workers develop asbestos-related diseases after about 10 years of exposure. Knowledge of asbestos, and occupational health and safety measures are almost nonexistent among the workers. Hospital staffs are unfamiliar with asbestos-related diseases, and misdiagnose the diseases at times. About 90 percent of domestic steel is produced in the ship-breaking operations in Bangladesh, which is an important contributor to national economy. Also, evidence suggests that asbestos-related diseases occur among workers after 30-40 years of exposure to asbestos in rubber industries in Bangladesh. Asbestos use is still growing in the country, and there are limited policies restricting its exposure. Scarcity of resource, inadequate coordination, ineffective monitoring and limited policy restricting exposure to asbestos are identified as the main challenges.

Conclusion: Using ecological intelligence and coping with the identified challenges to control human exposure to asbestos need to be bolstered through formulation and implementation of comprehensive pragmatic policy. It is imperative to conduct periodic health education and medical check-up of workers for prevention and control of asbestos-related diseases in Bangladesh.

Keywords: Asbestos, disease, ecology, Bangladesh

P064: Sex-differences and Gendered Experiences in Mesothelioma: Analysis of Asbestos Support Group Data in the England

Tod A¹, Senek M¹, Darlison L², Robertson S¹, Ejegi-Memeh S¹

¹University Of Sheffield, Sheffield, United Kingdom, ²University Hospitals of Leicester, Leicester, United Kingdom, ³HASAG, Southampton, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: Sex-differences in incidence, rates and survival from malignant mesothelioma are well documented. They often relate to men’s greater exposure to asbestos and women’s physiologically-based higher survival rates (e.g. Taioli et al, 2014). However, less well understood are sex and gender differences in initial symptom response, diagnosis experience, coping with treatment and disease progression, and experience of claiming benefits and compensation.

This paper presents early results from part of a wider study, the Gendered Experiences of Mesothelioma Study (GEMS). Specifically, this paper considers sex-differences in time from symptom onset to diagnosis; available support, claiming benefits and seeking legal advice.

Methods: We conducted analysis of routinely collected client data from an English Asbestos Support Group (HASAG). HASAG is a charity dedicated to helping people suffering from asbestos-related diseases and their families throughout the South of England, South East, London and Home Counties. Data was collected from 1177 clients and was divided into three sections based on the year that the persons mesothelioma was first reported to HASAG (2016, 2017,2018). We conducted an exploratory analysis to compare sex-differences in time from symptom onset to diagnosis; support available from next of kin; intention and
subsequent action in seeking legal advice, length of time to benefit claim.

**Results:** The majority of the 1177 cases were pleural mesothelioma (99%). There were 971 men (82.5%) and 206 women (17.5%) in the data set. There were more very young women in the cohort (<50yrs) than men (5% versus 0.5% of men). Women were more likely to have peritoneal mesothelioma (4% of Women vs 1% of Men).

It took longer for the female clients to be diagnosed with pleural mesothelioma than the men (153 days vs 184±230 days for women). The women also had a larger variation in the number of days from first symptom to diagnosis.

Men were more likely to have a next of kin than women (82.5% vs 75% of women). Therefore more women did not have the support of a close family member.

Women clients reported they were less likely to want to seek legal advice than men (35% of Women vs 18% of Men were Not Interested in receiving legal advice). Subsequently, there were differences in how many men and women actually went on to seek legal advice in each of the three years (Men: 87%-79%-75% vs Women: 70%-58%-51%)

On average, when claiming for compensation schemes administered by the UK government, men’s applications were awarded sooner than women’s (51±68 vs women 62±197).

**Conclusion:** These findings from the GEMS study provide unique insight into the sex-differences of a large cohort of people with mesothelioma in the South of England. The data demonstrate inequalities in terms of time to diagnosis, compensation payment and support from a close family member. This raises questions for health professionals about how to ensure care quality when assessing and supporting women with mesothelioma. Further research is required to understand the mechanisms at play which contribute to the sex-differences identified here.

**Keywords:** Mesothelioma, gender, diagnosis, social support
Conclusion: Among patients diagnosed with MPM in a single academic in the last three decades, despite changes in pleural effusion management, type of chemotherapy, and rates of surgery, disappointingly we found little change in overall survival. More research is needed to change the guarded prognosis associated with MPM.

P066: A Systematic Literature Review of Imaging Utilized for Diagnosis and Treatment of Malignant Peritoneal Mesothelioma

Carlson B¹, Armato S², Straus C²

¹Pritzker School of Medicine, University of Chicago, Chicago, United States of America, ²University of Chicago, Department of Radiology, Chicago, United States of America

Poster Session, Virtual, May 7, 2021

Objectives: Malignant peritoneal mesothelioma (MPeM) is a rare, aggressive tumor that has a poor prognosis. However, prognosis and treatment options may be improved with imaging advances in detection and assessment. Currently, it is unclear which imaging modality or protocol is the most clinically effective for these purposes. The objective of this study was to analyze the literature describing various imaging modalities used for peritoneal mesothelioma in order to determine their relative clinical efficacy. We also sought to review the most commonly reported imaging features of MPeM to promote a standardized reporting methodology so that results across studies can be combined.

Methods: We performed a systematic PubMed literature review of all original research articles (in English) from 1999 through 2019 that discussed the use of computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), or ultrasound with MPeM. The term “peritoneal mesothelioma” was searched with each modality listed along with a review of the reference lists of articles for additional capture of relevant literature. Publications that represented formal scientific study and reported effectiveness were analyzed in depth to isolate effectiveness of detecting MPeM. The effectiveness measures and common findings were then compared across imaging modalities. Given that a large percentage (50%) of published studies were case reports, a random sample of 100 case reports were analyzed in depth to ensure their findings reflected similar results.

Results: Among the 547 studies reviewed, 29 were retrospective or experimental studies that scientifically described imaging findings for MPeM. Amongst all 547 articles, CT was the most commonly reported imaging
modality used in disease detection and management (53%), followed by ultrasound (47%). MRI and PET were much less common (<15%). Individual studies have shown CT to perform with a diagnostic specificity of 100% and a sensitivity of 53%. PET has been shown to perform with a mild decrease in specificity (83-89%) and an increased sensitivity (86-92%), but no studies have analyzed the specificity or sensitivity of MRI, although it has been shown that MRI is the best predictor of peritoneal carcinoma index. The characteristics that have been shown to best differentiate MPeM from other disease included ascites, peritoneal thickening, mesenteric thickening, pleural plaques, maximum tumor dimension, and number of masses.

Conclusion: While CT is the most commonly used imaging modality in MPeM, research to date shows PET/CT and MRI to be the most promising. MRI is a particularly promising approach that has not been studied in adequate depth compared with CT or PET. Future MPeM imaging reports should highlight ascites, peritoneal thickening, mesenteric thickening, pleural plaques, maximum tumor dimension, and number of masses, given evidence of their importance. These changes will allow for better aggregation of MPeM imaging data across studies.

Keywords: Malignant Peritoneal Mesothelioma, imaging, diagnosis

P067: Computational Simulations to Determine the Safety and Efficacy of Tumor Treating Fields Delivered to the Lungs in Mesothelioma and NSCLC

Giladi M, Tiku K¹, Urman N¹, Naveh A¹, Bomzon Z¹
¹Novocure, Haifa, Israel

Poster Session, Virtual, May 7, 2021

Objectives: Tumor Treating Fields (TTFields), an anti-mitotic therapy utilizing low intensity, alternating electric fields in the intermediate frequency, are FDA-approved for glioblastoma and more recently for malignant pleural mesothelioma (MPM). This study investigates the efficacy and safety TTFields delivered to the lungs utilizing computational simulations. The phase 2 trial STELLAR trial (Ceresoli et al, Lancet Onc 2019; NCT02397928) has demonstrated promising extension of median overall survival in patients with MPM treated with TTFields plus standard of care chemotherapy. A phase 3 clinical trial [NCT02973789] is currently investigating the efficacy of TTFields therapy in Non-Small-Cell lung cancer (NSCLC). The efficacy of TTFields therapy depends on the frequency of the field; optimal frequency for MPM and NSCLC is 150 kHz. Delivery of an electric field to the body unavoidably leads to deposition of heat in the tissue. The higher the field intensity, the larger the therapeutic effect, with a therapeutic threshold of 0.7 V/cm above which TTFields exert a significant anti-mitotic effect. We performed numerical simulations to determine the thermal safety and the efficacy of TTFields to the torso.

Methods: Delivery of TTFields to the thorax of computational models using the NovoTTF-100L was simulated. Male and Female models (Virtual Population, IT’IS foundation) with BMI values ranging from normal to obese were used. Numerical simulations were performed using Sim4life (v3.0, ZMT Zurich). The field intensities within the lungs of the models were evaluated. Thermal safety was analyzed using specific absorption rate (SAR), which is a metric for assessing heating due to electromagnetic absorption.

Results: The simulations show that for all 3 models, the NovoTTF-100L device delivers TTFields at therapeutic intensities greater than 0.7 V/cm RMS to cover at least 76% of the lungs. SAR values within the internal organs are below the levels at which thermal damage occurs. In the superficial body layers, higher SAR values are observed. However, the NovoTTF-100L incorporates temperature control that prevents the skin from heating to levels at which thermal damage can occur.

Conclusion: The results of this study support the observations that the NovoTTF-100L delivers TTFields to the lungs at therapeutic levels and that the device is safe for use in MPM and NSCLC.
P068: Novel Diagnosis Technique for Identification of Asbestos Fibres in Mesothelioma Samples Using LA-ICP-MS Imaging

Voloaca O1, Clench M, Managh A, Cole L, Greenhalgh C, Haywood-Small S

1 Sheffield Hallam University, Sheffield, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: Malignant mesothelioma (MM) is an aggressive cancer of the mesothelium associated with occupational and environmental exposure to asbestos and other mineral fibres (MF). There is an urgent need to develop methods to clearly identify and quantify the MF within biological samples. The aim of the current project is to identify MF based on their metal content within MM in vitro models as well as patient samples using laser ablation-inductively coupled plasma-mass spectrometry imaging (LA-ICP-MSI).

Methods: MM models were developed using immortalised cell lines (NCI-H28, MSTO-211H) prepared as both 2D cytospins and 3D cell pellets. For the 2D samples, cells were exposed to 3 µg/mL MF solution (actinolite, amosite, wollastonite, crocidolite and chrysotile) for 24h and then harvested and cytospun onto glass or plastic slides. For the 3D cell pellets, 1 x 107 cells were harvested, centrifuged and treated with 100 µl MF before embedding in HMPC/ PVP media (3:1 ratio) and flash frozen in liquid nitrogen. The 3D models were cryosectioned onto either glass or plastic slides in 12 µm thick sections. Patient tissue samples were obtained from MesobanK (Cambridge, UK). LA-ICP-MS images were acquired using Thermo Scientific™ Element™ XR sector field ICP-MS Series instrumentation in standard measurement.

Results: Preliminary data has been acquired using LA-ICP-MSI, confirming that this analytical method has high potential in identifying the MF within cells. Moreover, data acquired in 2D models suggests that different MF can be identified based on shape, size and elemental composition. The MF were detected based on the high magnesium, iron and silicon content. Detection of calcium was attempted but requires further optimisation. Spatial distribution of the MF was also investigated in 3D models of MM by LA-ICP-MSI. Based on these findings, analysis on patient tissue will be performed to further validate this new approach in a clinical setting.

Conclusion: For the first time, this research has developed an imaging method using LA-ICP-MSI to identify MF within MM samples. High-resolution and high-speed analysis suggests that LA-ICP-MSI has the potential to be ultimately be integrated in clinical settings to aid early diagnosis of mesothelioma and higher overall survival rates.

Keywords: Mesothelioma, Mass Spectrometry Imaging, LA-ICP-MS
**P069: Ultrasound of the Chest in the Differential Diagnosis of Pleural Pathology and Mesothelioma**

Yuldoshev T

Tashkent Medical Academy, Tashkent, Uzbekistan

*Poster Session, Virtual, May 7, 2021*

**Objectives:** To study the echosemiotics of mesotheliomas, metastases and fatty suspensions on the pleura and to develop their differential diagnosis.

**Methods:** The study was carried out at the Tashkent Medical Academy No. 3, Tashkent, on ultrasound scanners of the middle class with sector and convex sensors of 3-6 MHz according to the original author's technique. We have developed and patented original methods of ultrasound diagnosis of mesothelioma in the anterior rib-phrenic sinus of the pleura with an assessment of its extrapleural distribution and focal formations on the mediastinal pleura and in the anterior rib-diaphragmatic sinus of the pleura with pleural effusion with differentiation of their benign or etiological. In total, more than 500 patients were examined, of which over 300 patients with varying severity of fibrinous pleural overlaps due to exudative pleurisy, hemothorax or pleural empyema, 105 patients with fatty pendants on the pleura, 50 patients with metastatic lesions and 45 with pleural mesothelioma.

**Results:** An X-ray examination was traditionally preceded by ultrasound. The fluid in the pleural cavity was anechogetic medium that was well-conducting ultrasound, in which various echogenic components of the effusion were clearly located: fibrin structures in the form of threads, partitions or networks, thickening of the pleura and volumetric formations on it. Mesotheliomas are characterized by a significant, more than 15-20 mm, uneven thickening of the most often the costal and diaphragmatic pleura, with a homogeneous hypoechoic structure and a predominant lesion of the anterior pleura with spreading to the anterior rib-diaphragmatic sinus in 33% of patients with its extension and germination in the caudal direction beyond the limits of the pleural cavity. For pleural overlays, a lesser degree of thickening of the pleura is characteristic, preservation of the anatomical acute-angled shape of the pleural sinuses, and dynamic echocardiography. Fat pendants are a normal anatomical element of the pleura, observed against the background of pleural effusion more often in patients with hypersthenic constitution, although they were also found in asthenics. They were detected in the anterior rib-phrenic sinus and on the mediastinal pleura along the contour of the ventricles of the heart, had a lobed rather echogenic structure, often elongated, while metastases were localized on any pleural sheet, had a hypoechoic homogeneous structure, round or flat. An important differential diagnostic criterion was the expressed transfer mobility of fatty suspensions during breathing and palpitations, in contrast to practically immobile metastases rigidly fixed on the pleura.

**Conclusion:** Ultrasound of the chest is a radiologically safe, simple and highly informative method of radiation diagnosis of pleural pathology, which allows to differentiate its tumor and inflammatory changes, as well as normal fatty suspensions and metastatics.

**Keywords:** metastases, fatty suspensions, mediastinal pleura, hemothorax, pleural empyema

**P070: Prediction of Response to ICI Treatment in Mesothelioma Using the eNose**

Disselhorst M, Wolf-Lansdorf M, de Vries R, Baas P

The Netherlands Cancer Institute, Amsterdam, Netherlands, *Breathomics, Reeuwijk, Netherlands*

*Poster Session, Virtual, May 7, 2021*

**Objectives:** To determine the predictive value of the eNose (volatile organic compounds VOC, Breathomics) in patients treated with Immune Checkpoint Inhibitors (ICI). Patient’s exhaled breath was analyzed for VOCs and correlated with the response to treatment. This is a prospective observational study and part of the INITIATE study reported this year (Lancet Respir Med. 2019 Mar;7(3):260-270)

**Methods:** Patients with recurrent MPM were treated with ipilimumab (1 mg/kg q 6 wks) plus nivolumab (200 mg flat dose q 2 wks) i.v. Response assessment was performed every 6 weeks with CT scanning. The clinical benefit was defined as SD or any response at 12 weeks.

**Results:** 35 patients were included in the study, one went off study before any treatment was given (median age 65 years;
27 males; 30 had epithelial histology). Of 31 patients, eNose data were available at start of the treatment. A Clinical Benefit was seen in 17 patients with 13 PR and 4 SD at 12 weeks. Progression was observed the other patients. The mPFS was 6.8 months and the mOS 22.8 months.

The three dimensional graph showed two clouds of data with some spatial distribution (figure 1). The ROC curve showed a value of 0.90 (CI 0.80-1.00) (figure 2).

**Conclusion:** The eNose was able to predict with high sensitivity and specificity the clinical benefit for patients treated with ICI in second line setting. Although no comparative group was available, our results are in line with the data observed in patients treated with ICI and Non Small Cell Lung Cancer (Ann Oncol 2019, Sept 17). Using exhaled breath analysis we can potentially identify responders and non-responders treated with IO therapy.

**Keywords:** MPM, Immune checkpoint inhibitor, prediction, eNose, volatile organic compounds

**P071: Involvement of the M-CSF/IL-34/CSF-1R Pathway in Malignant Pleural Mesothelioma**

Blanquart C1, D’Almeida S2, Tabiasco J3, Meiller C3,4, Chéné A1,5, Cellerin L1,3, Delayes S1, Delneste Y2,6, Fonteneau J1, Boisgerault N1, Bennouna J1,7, Grégoire M1, Jean D5,6, Blanquart C1

1CRCINA, INSERM, Université d’Angers, Université de Nantes., Nantes, France, 2CRCINA, INSERM, Université de Nantes, Université d’Angers., Angers, France, 3Centre de Recherche des Cordeliers, Sorbonne Universités, Inserm, UMR-1138., Paris, France, 4Functional Genomics of Solid Tumours, USPC, Université Paris Descartes, Université Paris Diderot, Université Paris 13, Labex Immuno-Oncology, Paris, France, 5Service d’Oncologie Médicale Thoracique et Digestive, Hôpital Laennec, CHU de Nantes, Nantes, France, 6Laboratoire d’Immunologie et Allergologie, CHU Angers., Angers, France, 7CHU de Nantes, oncoloie thoracique et oncologie digestive., Nantes, France

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer related to asbestos exposure. The tumour microenvironment content, particularly the presence of macrophages, was described as crucial for the development of the disease. This work aimed at studying the involvement of the M-CSF/IL-34/CSF-1R pathway, implicated in macrophage biology, in MPM, using samples from patients.

**Methods:** Pleural effusions (PE), frozen tumours, primary MPM cell and MPM cell lines used in this study belong to biocollections associated with clinical databases. Cytokine expressions were studied using real-time PCR and ELISA. The TCGA database was used as a complementary tumour collection to confirm our results. An original 3D co-culture model including MPM cells, monocytes from healthy donors and a tumour antigen specific cytotoxic CD8 T cell clone was used.

**Results:** We observed that high M-CSF or IL-34 levels in PE were associated with a shorter survival of patients. In tumours, expression of CSF1 was correlated with ‘M2-like macrophages’ markers whereas this was not the case with IL34 expression, demonstrating two distinct modes of action of these cytokines. Expression of IL34 was higher in patients with shorter survival.

**Keywords:** MPM, Immune checkpoint inhibitor, prediction, eNose, volatile organic compounds
in MPM cells compared to primary mesothelial cells. Particularly, high expression of IL34 was observed in MPM cells with an alteration of CDKN2A. Finally, using 3D co-culture model, we demonstrated the direct involvement of MPM cells in the formation of immunosuppressive macrophages through activation of the CSF1-R pathway causing the inhibition of cytotoxicity of tumour antigen specific CD8 T cells.

Conclusion: The M-CSF/IL-34/CSF-1R pathway is strongly implicated in MPM and could constitute a therapeutic target to act on immunosuppression and to support immunotherapeutic strategies.

Keywords: IL-34, M-CSF, mesothelioma, pleural effusions, biomarkers, macrophages

P072: Neo-antigen Vaccination and the Neo-antigen Response in Gemcitabine-treated Murine Mesothelioma

Boulter J1,2, Creaney J1,2,3,4, Robinson B1,4,5, Dick I1, Makwana N1,3, Neeve S1,3, Redwood A1,3

1National Centre for Asbestos Related Diseases, Perth, Australia, 2School of Biomedical Sciences, The University of Western Australia, Perth, Australia, 3Institute for Respiratory Health, The University of Western Australia, Perth, Australia, 4Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Australia, 5Medical School, The University of Western Australia., Perth, Australia

Objectives: Neo-antigens are expressed by cancers and encoded by tumour-specific mutated genes. Cancer vaccines incorporating neo-antigens have shown some clinical efficacy in melanoma. We are currently developing a clinical trial program to test neo-antigen vaccines for mesothelioma. In order to inform this program, we have been studying neo-antigens in our established murine mesothelioma model, AB1-HA. Previously, we identified two neo-antigens in this cell line; UQRC2 and UNC45a. The objectives of the current study were to:

i. evaluate the immunogenicity of candidate neo-antigens predicted using updated methods
ii. evaluate the effect of chemotherapy on the immune response to neo-antigens
iii. evaluate the efficacy of neo-antigen vaccines alone, and in combination with chemotherapy.

Methods: Candidate neo-antigens were predicted for the AB1-HA mesothelioma cell line following the identification of somatic single-nucleotide variants from whole-exome sequencing data using Mutect2. The MHC Class I binding affinity for overlapping peptides covering the mutation site was predicted using NetMHCpan4.0. Variants that were found to be expressed in RNA, had an IC50 of <500 nM, and/or a differential agretopicity index (DAI) >4 were selected for testing. To evaluate the immunogenicity of candidate neo-antigens, total cell preparations from spleen and lymph nodes of AB1-HA tumour bearing mice were exposed ex vivo to synthetic peptides corresponding to neo-antigens and the resultant IFNγ response was measured by ELISPOT assay. To determine the effect of chemotherapy on a neo-antigen response, we used gemcitabine which we have previously shown to be an immunogenic form of chemotherapy in mesothelioma. Thus, cells from gemcitabine treated AB1-HA bearing mice were screened for IFNγ responses against candidate peptides. Finally, to test the efficacy of neo-antigen vaccination, AB1-HA bearing mice were subcutaneously administered with three doses of neo-antigen peptide vaccine in adjuvant (poly I:C), with or without a single dose of gemcitabine intraperitoneally. Appropriate control groups were examined in parallel.

Results: A total of 180 neo-antigens were screened, in addition to the responses to the known neo-antigens UNC45a and UQRC2, immune responses to two novel neo-antigens, VMN2R67 and ELP2 was observed in cells from untreated tumour-bearing mice. Gemcitabine treatment of tumour-bearing mice did not alter the magnitude nor breadth of the immune response to predicted neo-antigens in cells from the draining lymph node or spleen. Vaccination of AB1-HA tumour-bearing mice with four endogenously recognised peptides (UQRC2, UNC45a, VMN2R67 and ELP2) did not affect tumour growth. Combining gemcitabine with poly I:C resulted in a significant delay in tumour growth, however the addition of neo-antigen peptides did not improve anti-tumour efficacy as compared to controls.

Conclusion: Our results indicate that gemcitabine does not increase the magnitude or breadth of the T cell
response to neo-antigens, however its application with other immune stimulants such as poly I:C may have therapeutic benefit.

Keywords: Neo-antigens, vaccine, chemotherapy, gemcitabine, murine mesothelioma

**P073: Efficacy of Salvage Chemotherapy Following Treatment with Immune Checkpoint Inhibitors in Mesothelioma Patients**

Calabro L¹, Grosso F², Daffinà M¹, Maconi A³, Di Giacomo A¹, Giannarelli D³, Maio M¹, Calabrò L¹

¹Center for Immuno-oncology, Medical Oncology and Immunotherapy, University Hospital of Siena, Siena, Italy, ²Mesothelioma Unit, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, ³Infrastruttura Ricerca Formazione Innovazione, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, ⁴Regina Elena National Cancer Institute, Rome, Italy

Poster Session, Virtual, May 7, 2021

**Objectives:** Therapeutic targeting immune checkpoint inhibitors (ICI) has proven effective in a variety of tumor types, and promising results have also been most recently reported in mesothelioma patients. However, only a proportion of mesothelioma patients achieved a long-term survival benefit with ICI therapy, and no information is available on the efficacy of chemotherapy in ICI-resistant subjects. Here we investigated the effectiveness of chemotherapy in mesothelioma patients who developed resistance to ICI.

**Methods:** This is a retrospective analysis in patients with pleural mesothelioma treated with salvage chemotherapy who progressed on ICI treatment. Progression-free survival (PFS) and overall survival (OS) were evaluated to assess the efficacy of post-ICI chemotherapy.

**Results:** From 2009 to 2019, 135 pleural and 5 peritoneal mesothelioma patients were treated with different ICI (i.e., tremelimumab, tremelimumab plus durvalumab, pembrolizumab, atezolizumab, ipilimumab plus nivolumab) in first (17%) or second/third line (83%), within clinical studies ongoing at two Italian Centers. Among these, 45 pleural mesothelioma patients, median (m) age 63.5 years (41-79), 13 female (28.9%), 32 male (71.1%), received sequentially chemotherapy after progressive disease to ICI. The remaining 95 patients did not receive chemotherapy for worsening of clinical condition, persisting disease control, because they received further immunotherapy, or were lost to follow-up. The most common cytotoxic agents used after ICI were platinum plus pemetrexed, vinorelbine, gemcitabine, gemcitabine plus imatinib, or pemetrexed. The mPFS of patients treated with chemotherapy was 5.3 months (95%CI.: 3.6 – 7.0), the mOS estimated from the beginning of chemotherapy was 8.3 months (95% CI.: 4.1-12.5). Interestingly, the mOS (12.2 months, 95% CI.: 5.5-18.9) of patients who had a secondary resistance to ICI was significantly (p=0.02) higher compared to that (6.8 months, 95% CI.:3.1-10.5) of patients who had a primary resistance to ICI; similarly, the 1-year survival of patients with a secondary and primary resistance to ICI was 51.0% and 11.1% , respectively.

**Conclusion:** Although preliminary, our results suggest that treatment of mesothelioma patients with salvage chemotherapy after ICI failure is clinically meaningful and represents a therapeutic option worth to further explore particularly in patients who previously benefitted from ICI therapy.

Keywords: immunotherapy, chemotherapy, mesothelioma

**P074: Analysis of Efficacy of Immunotherapy According to Histology in Malignant Pleural Mesothelioma (MPM) Patients**


¹Vall D’hebron University Hospital And Institute Of Oncology, Barcelona, Spain

Poster Session, Virtual, May 7, 2021

**Background:** MPM is a highly aggressive pleural tumor associated with asbestos exposure and with limited survival despite systemic therapy. In previously treated
patients (p), no-randomized studies of immunotherapy (ICI) have demonstrated activity, and Checkmate 743 demonstrated survival benefit of ICI in first line with some differences according to histology. The objective of this study is to characterize the impact of ICI use on survival in p diagnosed with MPM at our institution

**Methods:** We review 189 MPM p diagnosed at Vall d’Hebron University Hospital between November 2002 and April 2020. Associations between clinical variables and outcome were assessed with Cox regression models and survival data were calculated by the Kaplan-Meier method.

**Results:** Patient’s characteristics: median age 68 years (y) (45-88 y), males: 70%, performance status (PS)1: 69%, asbestos exposure: 74%, epithelioid subtype: 76%. First line chemotherapy was offered to 85% of p (66% cisplatin-pemetrexed and 27% carboplatin-pemetrexed) and 19 p were treated in clinical trials in first line. Median progression free survival (PFS) was 4.4 months (m;CI95% 3.1-5.4). Median survival (OS) in overall population was 21.3 m (95%CI17.2-24.3). Epithelioid histology, PS 0, neutrophil-lymphocyte ratio >5 and treatment with cisplatin vs carboplatin were associated with significant improvements in OS. In second line 27 p were treated with ICI in clinical trials. Median OS for p treated with ICI was 22.6 m (95%CI 11.1-34). No differences in PFS and OS for p treated with ICI were detected according to histology. Median PFS 2.7 m in epithelioid and 3 m in no-epithelioid (HRR0.7, p=0.00 CI95% 0.3-1.7) and OS 28.3 m in epithelioid and 13.8 m in no-epithelioid (HR3.4 p=0.01 CI95% 1.3-8.7). When we considered the OS of p treated with ICI from the time of initiation of the ICI the median OS for epithelioid p was 12.4 m vs 6.18 m for no epithelioid (HR2.1, p=0.09 CI95% 0.8-5.2).

**Conclusions:** In our series, ICI was an acceptable option for previously treated MPM patients. We confirmed histology is a prognostic factor with better OS for p with epithelioid tumors. However, we could not demonstrate histology is a predictive factor for efficacy of ICI.

---

**P075: Systematic Analysis of Chemoimmunotherapy Combinations That Lead to Durable Anti-tumour Responses in Murine Mesothelioma**

Chee J¹, Principe N¹, Chin W¹, Tilsed C¹, Fisher S¹, Jansen M¹, Dick I¹, Nowak A¹, Lake R¹, Chee J¹, Lesterhuis W²

¹University Of Western Australia, National Centre of Asbestos Related Diseases, Perth, Australia, ²Telethon Kids Institute, Perth, Australia

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Recent clinical trials investigating combination immune checkpoint blockade (ICPB) with chemotherapy have shown promising results with increased overall survival and progression-free survival in patients with non-small cell lung cancer. Combination ICPB and chemotherapy is an attractive option for the treatment of mesothelioma patients, and is currently being assessed by different groups including our own. Certain classes of chemotherapeutics are immunostimulatory. They induce immunogenic cell death, deplete immunosuppressive cell types within the tumour microenvironment, increase antigen cross-presentation and alter checkpoint ligand expression. Therefore, chemotherapy may prime an immune response that is further enhanced by ICPB, with the potential to convert non-responding patients into those that have an effective, durable anti-tumour response. However, it is unclear which classes of chemotherapeutics provide the most benefit in combination with ICPB. The cellular and immune mechanisms that underlie combination chemo-immunotherapy also need to be investigated to understand why some combinations may work well together, while others do not.

**Methods:** We investigated 12 chemotherapeutics from the main canonical classes dosed once at maximum tolerated dose in combination with ICPB (anti-CTLA-4 and anti-PD-L1) in two murine models of mesothelioma. Tumour growth and median survival between monotherapy and combination therapy were compared. Agonistic and antagonistic combinations, defined by analysis of hazard ratio’s (HR) were identified, and multi-parameter flow cytometry was performed to profile the tumour and tumour draining lymph node in best performing chemotherapy and ICPB combinations.

**Results:** We identified combinations that were synergistic, additive, provided no benefit or were antagonistic.
compared to monotherapy consistent in two models. In particular, fluorouracil (5-FU) or cisplatin was additive when combined with ICPB, whereas addition of vinorelbine to ICPB was antagonistic. 5-FU plus ICPB, the best performing combination, induced substantial expansion in the absolute number of lymphocytes within the tumour draining lymph nodes. The proportion of intratumoural, activated CD8+ T lymphocytes increased in 5-FU ICPB combination compared to 5-FU or ICPB monotherapy. Cisplatin ICPB combination increased the proportion of activated intratumoral CD4+ T helper lymphocytes compared to monotherapy. Anti-tumour responses in both combinations were CD8+ dependent. RNAseq analysis identified 5-FU ICPB treated tumours upregulated immune related genes and downregulated hypoxia and glycolysis signatures compared to monotherapies. In particular, 5-FU ICPB combination significantly enhanced IL-1 and TNFα signaling. We are currently confirming this mechanism, and results will be presented at the meeting.

Conclusion: We present a systematic assessment of therapy responses in different chemotherapy, ICPB combinations in murine mesothelioma models. Combination chemo-immunotherapy can be highly efficacious in murine mesothelioma models, and we identified synergistic therapeutic responses associated with activation of T lymphocytes and proinflammatory tumour microenvironments.

Keywords: checkpoint blockade, chemotherapy, combination therapy, T cells, murine models

P077: Transient Depletion of Regulatory T Cells after Non-ablative Hypofractionated Radiation Boosts Abscopal Responses in Murine Malignant Mesothelioma

Kohno M1,2, Murakami J2, Wu L2, Chan M2, Yun Z2, de Perrot M1,2

1Division of Thoracic Surgery, Toronto General Hospital, University Health Network, Toronto, Canada, 2Latner Thoracic Surgery Research Laboratories, Toronto General Research Institute, University of Toronto, Toronto, Canada

Objectives: Increasing evidence suggests that local radiotherapy (LRT) can elicit both local and systemic immune responses. Combining blockade of radiation-induced immunosuppressive responses with LRT may augment antitumor effects. Mice expressing a diphtheria toxin (DT) receptor under control of the Foxp3 locus (DEREG mice) allow conditional and efficient depletion of Foxp3+ regulatory T cell (Treg) by DT injection. This study aimed to elucidate the antitumor effect of transient depletion of Tregs combined with LRT in a murine malignant mesothelioma model.

Methods: The kinetics of various immune cells (T cells, Tregs, MDSCs, and macrophages) in the tumor microenvironment after LRT was examined by flow cytometry at different time points after nonablative hypofractionated radiation (5 Gy × 3 days) in a murine mesothelioma model. AB12 murine mesothelioma cells were injected s.c. into syngeneic DEREG mice and these mice were randomly assigned to one of the following treatments: 1) No treatment, 2) DT injection alone, 3) LRT alone, 4) combination of LRT and DT injection. To examine abscopal effects, AB12 were injected s.c. into DEREG mice at two separate sites, defined as a “primary” site that was irradiated and a “secondary” site outside the radiation field. Tissue samples were collected, and flow cytometry, immunofluorescent staining and quantitative RT-PCR were performed for analyses.

Results: The proportion of CD8+ T cells and Tregs of total CD45+ cells in tumors significantly increased in mice treated with LRT compared with those without LRT on 7 and 12 days after LRT. Selective depletion of Foxp3+ Tregs with LRT demonstrated synergistic antitumor effects compared with LRT alone (P = 0.009) and DT injection alone (P < 0.0001). Moreover, 60% of mice in the combination group showed complete responses. Immunofluorescent staining of the tumor showed Foxp3+ cells were higher in LRT alone, whereas CD3+ T cells were higher in the combination group. All mice that cured with LRT and DT injection rejected tumor re-challenge. Tumor-rejected mice had more central and effector memory CD4+ and CD8+ T cells. Both costimulatory molecules (ICOS, CD80, CD86, GITR) and coinhibitory molecules (CTLA-4, PD-1, TIM3) are upregulated at the mRNA level in the tumor in the combination group. Transient Treg depletion by DT injection after LRT showed the best tumor growth delay in both primary and secondary
tumor sites compared with LRT alone and DT injection alone. Total CD4+ and CD8+ T cells in spleen had no significant difference, whereas CD69+ activated CD4+ and CD8+ T cells increased in the group treated with LRT and DT injection. CD8+ T cells in spleen showed increased intracellular IFN-γ and Granzyme B production in mice treated with a combination of LRT and DT injection.

Conclusion: Accumulation of Tregs after LRT could be one of the reasons of the regrowth of the tumor after non-ablative hypofractionated radiation. Transient Treg depletion after LRT shows efficient local and systemic antitumor responses in murine mesothelioma. Upregulation of exhaustion markers on activated T cells suggests PD-1 or PD-L1 blockade after radiation and Treg depletion might be beneficial.

Keywords: mesothelioma, immunotherapy, radiotherapy, regulatory T cells, DEREG, abscopal effect

P078: Oncolytic Viruses in Malignant Pleural Mesothelioma

Ledhar P1, Nastase A1, Macfarlane M1, Willis A1, Harrington K2, Melcher A2, Moffatt M1, Cookson W1

1Imperial College London, London, United Kingdom, 2Institute of Cancer Research, London, United Kingdom, 3MRC Toxicology Unit, Cambridge, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: Malignant Pleural Mesothelioma is an aggressive cancer of the serosal membranes, with a poor median survival of 9-12 months. Oncolytic viruses are a form of next-generation therapy. They are able to directly lyse cancer cells and prime the immune system. In this project we aimed to assess the effects of Reovirus, Herpes Simplex virus 1716 (HSV1) and Maraba virus on two commercial and 8 primary mesothelial cell lines that have been whole genome sequenced.

Methods: Cells were seeded at 4000 cells per well and infected after 24 hours with predetermined molarities of infection (MOIs, range 0.000256-10) of viruses. MTT viability assays were conducted at 24, 48 and 72 hours post-infection.

Results: ANOVA showed significant changes in viability at all 3 time-points for the commercial biphasic cell line (MSTO-211H) treated with Maraba (P<0.0001), with MOIs as low as 0.0032. ANOVA was significant at Day 2 for the sarcomatoid cell line (NCI-H2052) at MOI of 10. HSV1 showed significant effects only on the commercial biphasic cell line at Day 2 for MOI of 10. Reovirus did not show any significant effects on commercial cell lines. Maraba virus showed significant effects in all 8 primary cell lines treated by day 3, particularly at higher MOIs.

Conclusion: Investigation of discrepancies in the cell-lines’ responses, infectivity and viral replication are underway and may be attributed to underlying genetic defects. These findings present a good foundation upon which to conduct future research, including comparison with the Superior Killing Virus (SKV).

P079: Nivolumab in a Patient with Malignant Pleural Mesothelioma Resulting in Persistently Elevated Troponin Levels Despite Clinical Remission of Myocarditis and Myositis: A Brief Report

Lie G1, Weickhardt A1,2,3, Kearney L4, Lam Q5, John T1,2,3, Liew D4,7, Arulananda S1,2,3

1Department of Medical Oncology, Olivia Newton-John Cancer and Wellness Centre, Heidelberg, Australia, 2Cancer Immuno-Biology Laboratory, Olivia-Newton John Cancer Research Institute, Heidelberg, Australia, 3School of Cancer Medicine, La Trobe University, Heidelberg, Australia, 4Department of Cardiology, Austin Health, Heidelberg, Australia, 5Department of Pathology, Austin Health, Heidelberg, Australia, 6Department of Rheumatology, Austin Health, Heidelberg, Australia, 7Department of Medicine, University of Melbourne, Parkville, Australia

Poster Session, Virtual, May 7, 2021

Objectives: Malignant pleural mesothelioma (MPM) is a rare and highly lethal malignancy associated with poor prognosis. frontline therapy with cisplatin, pemetrexed and bevacizumab combination chemotherapy improved overall survival. However, there is no approved second line treatment for MPM. Several phase II trials on MPM patients have demonstrated approximately 40% disease control rate with immune checkpoint (ICI). We hereby report a patient with
MPM from our institution who developed severe immune-related myositis and myocarditis following treatment with nivolumab therapy and achieved an impressive but short-lived anti-cancer response.

Results: A 79 year old man was diagnosed with right sided PD-L1 negative epithelioid MPM and underwent VATS pleurodesis, followed by six cycles of carboplatin and pemetrexed chemotherapy. His disease progressed on maintenance pemetrexed and he was switched to nivolumab therapy. He presented with sudden onset of severe proximal limb, truncal weakness and generalized fatigue after 2 cycles of nivolumab. Subsequent testing revealed a creatine kinase (CK) of 6602 units/L (reference interval 20-200) and high sensitivity troponin T (hsTnT of 1072 ng/L (reference interval <15) (Figure1). Electrocardiogram (ECG) and transthoracic echocardiogram (TTE) were normal. A muscle biopsy performed showed necrotizing myositis. A diagnosis of immune-mediated myositis and myocarditis was made.

Treatment was initiated with high dose IV methylprednisolone 1000mg with rapid improvement of proximal myopathy. The patient’s CK level significantly decline within days, however, hsTnT levels remained persistently high, despite no florid clinical features of myocarditis. In an attempt to understand the lack of concordance between his CK and hsTnT levels, troponin I were measured across 3 different assays. The results were consistent with our laboratory findings with elevated troponin I and raised NT-pro BNP levels, suggesting cardiac involvement. A cardiac MRI performed showed evidence of myocarditis with patchy enhancement in the basal and mid inferolateral segments. Mycophenolate mofetil was added as a steroid sparing agent, with weaning prednisolone regime over an 8-week period. Restaging PET/CT scan following 2 cycles of nivolumab showed a near complete metabolic remission. Despite resolution of symptoms, the patient was not rechallenged with nivolumab due to subclinical myocarditis.
ABSTRACTS

Unfortunately, radiological remission was not sustained. Repeat PET/CT scan 3 months following the last dose of nivolumab showed progression of pleural effusion and pleural nodules. The patient remained clinically well and was commenced on third line vinorelbine chemotherapy.

**Conclusion:** This report illustrates an unusual case of biochemical discordance with persistent markedly elevated troponin levels despite the absence of symptoms and a normal CK in a patient with myositis and myocarditis irAEs. Clinicians should be aware that myositis irAE is associated with cardiac irAE and patient presenting with myositis, should be screened for cardiac involvement even in the absence of symptoms. The association of troponin level with myocardial damage in immune checkpoint inhibitor associated myocarditis is not clearly understood. More robust monitoring of serological activity including cardiac troponin levels in patients being treated with immune checkpoint inhibitors may help to identify subclinical myocarditis and guide treatment response.

**P080: Combined Immune Checkpoint Blockade: In Vivo Validation of In Vitro Results**

Marcq E1, Van Audenaerde J1, De Waele J1, Merlin C1, Pauwels P1,2, Fisher S3,4, van Meerbeeck J1,5, Smits E1,6

1University Of Antwerp - Centre for Oncological Research, Antwerp, Belgium, 2Department of Pathology - Antwerp University Hospital, Antwerp, Belgium, 3National Centre for Asbestos Related Diseases (NCARD) - The University of Western Australia, Perth, Australia, 4School of Biomedical Sciences - The University of Western Australia, Perth, Australia, 5Department of Pulmonology - Antwerp University Hospital, Antwerp, Belgium, 6Centre for Cell Therapy and Regenerative Medicine - Antwerp University Hospital, Antwerp, Belgium

**Objectives:** Malignant pleural mesothelioma (MPM) is an aggressive cancer that is causally associated with asbestos exposure. Due to its aggressive nature and despite the effectiveness of conventional anti-cancer treatment, the prognosis of patients diagnosed with MPM remains dismal. Data from us and others on the presence of the immune checkpoint-related molecules PD-1, PD-L1, TIM-3 and LAG-3 in MPM lay the basis to evaluate their suitability as immunotherapeutic targets. It is of great interest to investigate the effect of combined treatments and compare them to stand-alone treatment to select the best therapeutic strategy for MPM.

**Methods:** Human cell lines representative for the epithelioid (NCI-H2818 and NCI-H2795) and sarcomatoid (NCI-H2731) subtypes of MPM were placed in allogeneic co-cultures with healthy donor peripheral blood mononuclear cells. The co-cultures were treated with anti PD-1 or anti PD-L1 in combination with anti TIM-3 or anti LAG-3. Supernatant was collected and enzyme-linked immunosorbent assays and multiplex electrochemo-luminescence were used to assess the secretion of 7 cytokines; IFN-γ, IL-2/5/6/10, IL-1β and TNF-α, as well as the enzyme granzyme B. Statistical analysis was done to investigate the differences between the treatment conditions. Our in vitro results were validated in vivo using the AB1-HA BALB c/J mesothelioma mouse model. Tumor cells were injected subcutaneously and immune checkpoint blocking antibodies were injected intraperitoneally.

**Results:** Treatment with immune checkpoint blockers as monotherapy or in combination resulted in a significant increase in the secretion of granzyme B and the cytokines IFN-γ, IL-2, IL-5 and IL-10. Although the increased secretion was not always statistically significant for all 3 MPM cell lines of the two subtypes, the same trends were observed among them. Interestingly, highest concentrations of granzyme B and these 4 cytokines were noticed for monotherapy treatment with anti PD-1, anti PD-L1 or either of these antibodies with anti TIM-3. Statistical analysis showed that there was no significant difference between PD-1 or PD-L1 monotherapy and their combination with anti TIM-3 or anti LAG-3. Our in vivo data are in line with our in vitro findings, showing a significant survival benefit for mice treated with anti PD-L1.

**Conclusion:** Statistical analysis showed that TIM-3 or LAG-3 blockade had no added value to PD-1 or PD-L1 monotherapy in vitro. These findings were confirmed in vivo. PD-L1 blockade resulted in a significant survival benefit in the AB1-HA mesothelioma mouse model while there were no significant effects for TIM-3 or LAG-3 blockade. These data support the idea to look beyond combined immune checkpoint blockade and to investigate the combination of anti PD-L1 with other treatment strategies.

**Keywords:** Immune checkpoint blockade, in vivo, in vitro
P081: Identifying Prognostic Immune Biomarkers in Patients with Malignant Mesothelioma

McDonnell A1,2, Principe N1, Chee J1, Cook A1, Creaney J1, Robinson B1, Lee Y3,4, Waithman J2, Lake R1, Nowak A1,5

1National Centre for Asbestos Related Diseases, Perth, Australia, 2Telethon Kids Institute, Perth, Australia, 3Institute for Respiratory Health, Perth, Australia, 4Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Australia, 5Department of Medical Oncology, Sir Charles Gairdner Hospital, Perth, Australia

Poster Session, Virtual, May 7, 2021

Objectives: T cells are essential to an effective anti-tumour immune response, however there is minimal information regarding whether T cell subsets at the tumour site are distinct from those in circulation. Pleural effusions associated with malignant mesothelioma contain tumour cells, lymphocytes and cytokines, thus providing a unique opportunity to serially sample immune events at the tumour site. Using pleural fluid as a surrogate for the tumour microenvironment, we have characterised T cell populations at the tumour site compared with peripheral blood in patients with mesothelioma.

Methods: Pleural effusion and matched peripheral blood was collected from 31 patients with mesothelioma. Mononuclear cells were enriched by ficoll gradient centrifugation and T cell populations analysed by flow cytometry and evaluated for association with patient survival.

Results: Pleural effusion CD8+ and CD4+ T cells displayed a dysfunctional phenotype with increased expression of PD-1, TIGIT, LAG-3 and Tim-3 compared to blood. PD-1 was the receptor most overexpressed on all T cells in the blood and pleural effusions. Co-expression of inhibitory receptors was greatest on CD8+ T cells in pleural effusion and restricted to cells bearing a tissue resident memory T cell phenotype (CD69+ CD103+/−) that were absent from the blood. Further analysis revealed that the proportion of CD8+ T cells in pleural effusion that were CD69+CD103+ positively correlated with overall survival. In line with this, higher proportions of CD8+CD69+CD103+ T cells were associated with improved survival in univariate analysis. We are currently analysing multiple T cell phenotypes for their association with patient outcome using multivariate analysis. Results will be presented at the meeting.

Conclusion: Pleural effusion T cells are thus distinct from those circulating in peripheral blood and provide a less invasive means of monitoring T cells at the tumour site than serial biopsy. Tissue resident memory T cells in malignant pleural effusion are a potential source of tumour-reactive T cells that can predict for outcome in patients with mesothelioma.

P082: Microfluidic Based Analysis of MPM-Tumor Infiltrating Lymphocytes Interaction

Oliveto S1, Ritter P1, Miluzio A1, Rossi R1, Gruarin P1, Curti S1, Benvenuti M2, Novellis P3, Veronesi G3, Raimondi M4, Pagani M5, Biffo S1,6

1INGM, Istituto Nazionale di Genetica Molecolare “Romeo ed Enrica Invernizzi”, Milan, Italy, 2Department of Cardio-Thoracic Surgery, Spedali Civili, Brescia, Italy, 3Division of Thoracic Surgery, San Raffaele Scientific Institute, Milan, Italy, 4Politecnico of Milan, Milan, Italy, 5IFOM, Milan, Italy, 6DBS, Department of Biosciences, University of Milan, Milan, Italy

Poster Session, Virtual, May 7, 2021

Objective: Development of a microfluidic-based scaffold for studying MPM-TILs interaction from human samples; Isolation and molecular characterization of intratumoral CD4+ Tregs from surgical chemonaive MPM samples.

Methods. 1. MPM samples are plated in a special matrix and cells cultures are established. 2. We microengineered a 3D scaffold that hosts tumoral cells derived from MPM biopsies via a two-photon laser polymerization (2PP) technique. 3. Chemonaive MPM samples are collected (n=10) and infiltrating CD4+ Tregs are subjected to RNA-sequencing, in comparison to matched blood Tregs and NSCLC infiltrating Treg cells. 4. We characterized Tregs molecular signature and immune microenvironment.

Results. We obtained high efficiency in maintaining primary MPM cells, which retrieve native tumors. Primary lymphocytes are circulated by a microfluidics pump on
the tumor scaffold where they are maintained alive and some are able to adhere. We show that MPM are highly infiltrated with CD4+ Tregs which are spread in the tissues. Foxp3+ cells are specifically organized in the infiltrates’ periphery and have high immunosuppressive capabilities. Transcriptional analysis shows that Tregs upregulate several immunosuppressive genes and a specific set of cytokines and cytokine receptors. Surprisingly, they expressed also a set of genes never described, underlining the uniqueness of the immunosuppression in MPM. Moreover we identified enriched genes in translation processes and ribosomal subunits component.

**Conclusion.** Immunesuppression is part of the developmental program of MPM tumor cells. Manipulation of tumor-derived signals targeting specific Treg cells may ameliorate MPM therapies and treatment.

**Objectives:** Neo-antigens are tumour proteins that are derived from a mutation of the tumour genome and can be recognised by the immune system. In early-phase clinical trials, a neo-antigen peptide vaccine has demonstrated some encouraging results. However, there is no empirical data to support which neo-antigen peptides are the best vaccine targets. We are therefore using our established murine mesothelioma model, AB1, to predict and identify neo-antigens that can be used as best vaccine targets. Previously, we identified two neo-antigens in this cell line; UQRC2 and UNC45a that are immunologically recognised by cells of tumour-bearing mice. However, there are many in silico predicted “strong” neo-antigens which are not recognised in tumour-bearing mice, which raises several questions, including whether there is a T cell repertoire for these antigens. The objective of this study was to identify neo-antigen candidates that can induce an immune response and to compare the efficacy of vaccination with either immunogenic or non-immunogenic neo-antigens in a prophylactic murine mesothelioma model.

**Methods:** Naive Balb/c mice were immunized with two doses of predicted neo-antigen peptides. Seven days later draining lymph nodes were harvested and cells were exposed ex vivo to synthetic peptides corresponding to neo-antigens and the resultant IFNγ response was measured by ELISPOT assay. Peptides that induced cells to produce IFNγ upon restimulation were classified as immunogenic. Subsequently, naive mice were vaccinated with different combinations of immunogenic and non-immunogenic peptides, and appropriate controls. Peptides were administered subcutaneously at three-time points along with an adjuvant poly I:C before tumour inoculation.

**Results:** Immunisation of mice with the long neo-antigen peptides resulted in an immune response being generated to 63% (19/30) of the tested neo-antigen candidates. Vaccination of mice with either ten immunogenic or ten non-immunogenic peptides did not significantly affect tumour
growth. An increase in the breadth of an immune response (IFNγ production) was observed in tumour-bearing mice following vaccination with immunogenic peptides.

**Conclusion:** Neo-antigen specific T cell responses were directed against a sub-set of candidate neo-antigens. A neo-antigen vaccine could boost the immune response however; it could not protect mice from developing mesothelioma. The strategy of combining neo-antigen vaccines with other immune-modulators such as checkpoint blockade may enhance immunogenicity and achieve better clinical outcomes.

**Keywords:** Neo-antigens, vaccine, peptides, T-cells

---

**P084: Evaluation of Host T Cell Responses to Genomically Predicted MM Neo-antigens**


1 National Centre For Asbestos Related Diseases, Australia, 2 Department of Respiratory medicine, Sir Charles Gairdner Hospital, Australia, 3 Queensland Institute of Medical Research, Australia

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant mesothelioma (MM) is partially susceptible to immunotherapy. The reason for failure of immunotherapy remains unclear but one possibility is that there is a weak pre-existing anti-mutation ('neo-antigen')-specific immune response. Thus, therapies such as Immune Checkpoint Blockade (ICPB) that release the brakes on the immune response have nothing to release. Identifying neo-antigen reactivities might provide accurate methods of tracking specific anti-MM immunity which could facilitate treatment decision making, and also inform the development of neo-antigen vaccines to boost anti-MM immunity.

**Objective** is to evaluate host T cell responses to genomically predicted MM neo-antigens.

**Methods:** Predicted HLA Class I neo-antigenic peptides were determined by whole exome/RNA seq and selected based on MHC affinity (IEDB; IC50), expression (RNAseq) and differential aggretopicity index (DAI). MM patient blood and pleural effusion T cell responses to these predicted neo-antigenic peptides were evaluated using ELIspot following initial 'supervised' neo-antigenic peptide-driven expansion (Figure).

**Results:** Low level spontaneous responses were seen, as in other cancers. In one patient a T cell response to a mutated peptide was seen in both blood and pleural fluid (a cysteine to phenylalanine mutation at anchor residue 2 of peptide CFDPPLTRM) whereas in another the response to a predicted neo-antigen was only found in the effusion T cells (a valine to glycine mutation at anchor residue 9 of peptide ATARLPQRG).

Peptide mapping of minimal epitopes determined the optimal peptide characteristics and HLA restrictions (HLA-C04:01 and HLA-A02:01) from the set of bioinformatically predicted possibilities.

**Conclusion:** T cells responding to MM mutations can be found in patients and malignant effusions may identify more of such reactivities. Such an approach provides evidence for genuine neo-antigens which can then be a) reverse engineered for the analysis of host T cell responses as therapy biomarkers e.g. using multimers and/or T cell receptor patterns, and b) for neo-antigen vaccines as an additional form of MM immunotherapy.
P085: Monitoring Neo-antigen Responses Can Inform MM Therapy

Creaney J1,2, Forbes C1,2, Chee J1,2, Shaokang M1,2, Neeve S1,2, Boon L, Celliers L3, Fisher S1,2, Dick I1,2, Nowak A1,4, Creaney J1,4, Robinson B1,4

1National Centre For Asbestos Related Diseases, Australia, 2School of Biomedical Sciences, The University of Western Australia, Australia, 3Australian Cancer Research Foundation, Australia, 4Sir Charles Gairdner Hospital, Australia

Poster Session, Virtual, May 7, 2021

Objectives: Immunotherapies are effective in some MM patients. Tumour neo-antigens are likely the main targets for attack. Given that, we tested whether responses to neo-antigens in a murine model of MM are:

a) sensitive enough to determine post-surgical recurrence prior to positive imaging, and

b) able to predict responses to immune checkpoint blockade (ICPB) therapy.

Methods: To examine this, we interrogated the immune response to tumour neo-antigens in BALB/c mice bearing the AB1-HA MM model

a) To identify MM neo-antigens AB1-HA whole exome sequencing and RNAseq data were analysed and the MHC-I binding affinity of mutated sequences were predicted and expression confirmed with RNA-seq data.

b) To detect post surgical recurrence tumours were surgically resected on day 14 and injected iv with luciferase transfected cells (AB1-HA_LUC cells). Lung tumour growth was determined sequentially by an In Vivo Imaging System (IVIS) and imaged for peak bioluminescence in a Lumina II Imager (Figure), PET-CT (IV 15-FDG at 7-15MBq). For neo-antigen specific T cell detection, IFNg ELISPOT assays were performed

c) To determine if pre-treatment neo-antigen responses are able to predict responses to ICPB, we utilised a version of the dual-tumor model developed by Lesterhuis et al. Tumours and dLNs were resected and subsequent ICPB blockade administered (100 μg anti-CTLA-4 and 50 μg anti-GITR, doses that induced ~50% tumour regression), enabling retrospective analysis of the dLN neo-antigen responses in subsequent responders and non-responders. Neo-antigen responses were examined as above.

Results:

a) Neo-antigens: We identified UQCRC, UNC45, with HA, as neo-antigens.

b) Recurrence: A combination of 3 neo-antigen specific T cell responses increased the sensitivity of metastasis detection, prior to evidence of tumour recurrence on IVIS or PET-CT. Combination of the 3 neo-antigen specific T cells were strikingly increased in frequency, 85.96±11.45 SFU/100,000 cells for the recurrence group compared to 17.21±4.57 SFU/100,000 cells for healthy lungs in the non-recurrence group, (p<0.0001).

c) Strong dLN responses to UNC45a prior to ICPB therapy predict successful treatment outcome. Pre-treatment dLN UNC45a response was significantly higher in the responders (24 ± 14 SFU/105 vs 5 ± 2 SFU/105, p = 0.0004). This suggests that responses to some neo-antigens could predict subsequent response to ICPB therapy.

Conclusion: Neo-antigen specific T cell responses increases sensitivity of recurrence/metastasis detection and predict ICPB therapy outcome. These observations suggest a novel biomarker approach to the clinical assessment of early recurrence and the prediction of ICPB response.
**P086: Characterization of Immune Microenvironment in Primary Tumor and Tumor-involved Lymph Nodes from Patients with Malignant Pleural Mesothelioma: A Pilot Study**

Mangalick K¹, Mezzano V², Loomis C²⁻³, Moreira A³, Pass H⁴, Sterman D⁴⁻⁵

¹NYU School of Medicine, New York, United States, ²NYU School of Medicine, Experimental Pathology Research Laboratory, New York, United States, ³NYU Langone Health, Department of Pathology, New York, United States, ⁴NYU Langone Health, Department of Cardiothoracic Surgery, New York, United States, ⁵NYU Langone Health, Division of Pulmonary, Critical Care and Sleep Medicine, New York, United States

**Poster Session, Virtual, May 7, 2021**

Objectives: Malignant pleural mesothelioma has a poor prognosis with median survival of 12-24 months. We are not aware of any studies examining the immune microenvironment in the tumor draining lymph nodes (TDLN) of these patients. Our aim is to characterize interactions between key immune cells and mesothelioma. We hypothesize that tumor-involved areas of lymph nodes will be immunosuppressive in comparison to healthy lymph node tissue and impact the immune response in the primary tumor.

**Methods:** We performed multiplex immunolabeling on stored primary tumor and nodal biopsy specimens from 3 patients from our tumor bank for a pilot study. Image analysis was performed using InForm® (Akoya Biosciences). Tissue was classified as “tumor” or “non-tumor” using semi-automated segmentation based on pan-Cytokeratin (panK) labeling. Cellular phenotypes were defined by surface markers: regulatory T-cells (Tregs) (CD3+/FOXP3+), cytotoxic T-cells (CD3+/CD8+), and tumor cells (panK+). Cellular populations in each tissue region were quantified. Nearest neighbor analysis was used to approximate cellular interactions by measuring distances between Tregs or cytotoxic T-cells and tumor cells.

**Results:** The bordering “non-tumor” lung tissue of primary tumor biopsies had higher concentrations of Tregs (0.30% vs 0.16%) and cytotoxic T-cells (1.86% vs 0.55%) than corresponding “tumor” regions (P=0.04 for both). Nodal non-tumor regions had higher concentrations of cytotoxic T-cells (3.83% vs 3.71%) and lower concentrations of Tregs (0.55% vs 1.34%) than tumor regions (P=0.36 and 0.18, respectively). Nearest neighbor analysis revealed shorter distances to the nearest tumor cells for Tregs.
(17.24 vs 32.64µm, P<0.01) and cytotoxic T-cells (18.76 vs 33.24µm, P<0.01) in lung tumor vs non-tumor regions and longer distances for Tregs (75.92 vs 74.12µm, P=0.37) and cytotoxic T-cells (76.37 vs 65.85µm, P<0.01) in nodal tumor vs non-tumor regions.

Conclusion: Multiplex immunolabeling is feasible in stored mesothelioma specimens, allowing the utilization of quantitative immunopathology to study corresponding immune microenvironments. Greater numbers of Tregs and cytotoxic T-cells in non-tumor versus tumor regions of primary tumor biopsies may suggest a T-cell excluded phenotype. Proximity of Tregs and cytotoxic T-cells infiltrating the tumor regions to the nearest tumor cell could indicate immunosuppressive interaction between tumor cells and Tregs. In the TDLNs, cytotoxic T-cells were further from the nearest tumor cell in tumor regions versus non-tumor regions, possibly mirroring immunosuppressive cellular interactions in primary tumors.

This pilot analysis is the first to preliminarily characterize tumor-involved nodal tissue in mesothelioma in relation to healthy nodal tissue and primary tumors.

Funding: Mesothelioma Applied Research Foundation

Keywords: Mesothelioma, immunology, immune microenvironment, tumor-draining lymph node, T-cell, immunopathology, immunolabeling

**P087: Salvage Ipilimumab and Nivolumab in Patients with Anti-PD-1-resistant Malignant Pleural Mesothelioma**

Szlosarek P1,2, Shamash J2, Tuthill M4, Sheaff M2, Houghton D1, Skaria S1,3

1Barts Cancer Institute, Queen Mary University of London, City Of London, United Kingdom, 2Barts Health NHS Trust, City of London, United Kingdom, 3Ramsay Healthcare, Sawbridgeworth, United Kingdom, 4Oxford University Hospitals, Oxford, United Kingdom, 5East Sussex and North Essex NHS Foundation Trust, Colchester, United Kingdom

**Objectives:** PD-1/PD-L1 immune checkpoint blockade has activity in mesothelioma with disease control rates of 70-80% and a median overall survival of 12-18 months. Here, we document the efficacy of ipilimumab and nivolumab in patients that have failed PD-1 inhibitor monotherapy.

**Methods:** Demographics, prior treatment, PD-L1 expression, response, toxicity and survival outcome data were collated on ten consecutive patients treated with ipilimumab and nivolumab following progression on pembrolizumab or nivolumab from two hospitals in the UK. Nine patients received 1mg/kg of ipilimumab every 6 weeks and 3mg/kg nivolumab every two weeks on a 6 weekly cycle; one patient with multiple brain metastases received 3mg/kg ipilimumab every 6 weeks and 3mg/kg nivolumab every two weeks on a 6 weekly cycle.

**Results:** Between March 2018 and October 2019, ten patients (9 male and 1 female), aged 58-75, were treated with ipilimumab and nivolumab with assessment of response by mesoRECIST. Histology: epithelioid (n=7) and biphasic (n=3) subtype only. Performance status: 1 (n=6); 2 (n=3) and 3 (n=1); two patients had brain metastases. Prior treatment was with pembrolizumab (n=9) or nivolumab (n=1). Clinical benefit was observed in 4 of 9 (or 44%) evaluable patients, including an improvement in performance status and palliation of symptoms. MesoRECIST response assessment to date is as follows: 1 partial response, 1 stable disease, 1 mixed response (in patient with brain metastases receiving 3mg/kg dose of ipilimumab), 4 progressive disease, 1 non-evaluable, and 2 awaiting CT assessment. Grade 3 colitis was noted in 2 patients (20%) and responded to an oral steroid taper. Median overall survival is 4 months (range: 1-10 months) with 3 patients remaining on ipilimumab and nivolumab therapy. PD-L1 biomarker assessment is ongoing.

**Conclusion:** Based on this small cohort, salvage ipilimumab and nivolumab displays activity in 40-50% of patients progressing on prior anti-PD1 monotherapy. Clinically meaningful responses were seen in anti-PD1 resistant patients and treatment was generally well-tolerated. Larger studies are warranted to define patient selection and to further optimise ipilimumab and nivolumab for relapsed mesothelioma.
**P088: Contribution of Immunosuppressive Lymphocytes in Mesothelioma Cancer Development**

**Tone M**, **Tone Y**, **Nguyen M**, **Fua-Feng L**, **Cameron R**

1Pacific Heart Lung And Blood Institution, Los Angeles, United States, 2UCLA, Los Angeles, United States

**Poster Session, Virtual, May 7, 2021**

**Objectives:** To develop immunotherapy strategies for mesothelioma, we have been investigating immunosuppressive cells and mechanisms in mesothelioma tumors. The immune system protects us not only from foreign invaders, such as bacteria and viruses, but also from cancer cells. However, some cancer cells utilize immunosuppressive mechanisms and evade the anti-tumor immunity. To eradicate these cancer cells, we can enhance the anti-tumor immunity by blocking key immunosuppressive mechanisms in these cancer patients. To identify which immunosuppressive systems are exploited by mesothelioma cells and by different types of cancer cells that we used as controls, we have analyzed immune cell populations in mesothelioma and lung cancer tumors using flow cytometry. PD-1/PD-L1 immunotherapy also blocks PD-1-mediated immunosuppression and has been recently highlighted as an effective cancer treatment. To assess efficacy of PD-1/PD-L1 immunotherapy in mesothelioma patients, we have also analyzed PD-1 and PD-L1 expression levels in these patients.

**Methods:** To investigate cancer type-specific immunosuppressive mechanisms, we analyzed tumors from two different types of cancers, mesothelioma and lung cancer. Mesothelioma is a rare cancer (about 3,000 new cases per year in the US) that normally takes 20 to 50 years to develop. On the other hand, lung cancer is one of the most common (about 230,000 new cases per year in the US) and fast-growing cancers. Single suspension cells were prepared from 34 mesothelioma and 18 lung cancer tumors. Immune cell populations in these tumors were analyzed by flow cytometry using antibodies against immune cell-specific marker proteins and PD-1/PD-L1.

**Results:** To assess anti-tumor immune responses in mesothelioma and lung cancer tumors, we have investigated T cell activation/proliferation in these tumors. Both CD4+ (helper) and CD8+ (cytotoxic) T cell populations were expanded in almost all tumors tested, suggesting that these T cells responded to these cancer cells. Further analysis of T cell activation status also suggests that many of these T cells were memory/exhausted T cells that had lost their direct cancer-killing activities. We subsequently analyzed PD-1-mediated T cell inactivation in these tumors and revealed that PD-1/PD-L1 was not a major immunosuppression mechanism in many of the mesothelioma tumors tested. To investigate how T cell mediated anti-tumor activity was blocked, we further investigated immunosuppressive FOXP3+ regulatory T cell (Treg) and M2-macrophage populations in mesothelioma and lung cancer tumors. Both immunosuppressive cells were increased in mesothelioma tumors. Particularly, Treg populations were increased in a cancer stage-dependent manner in these tumors, suggesting that Treg is strongly involved in mesothelioma cancer development. In contrast, Treg populations were high in Stage1 lung cancer tumors, but were, surprisingly, significantly decreased in Stage2 and Stage3 lung cancer tumors.

**Conclusion:** Both Treg and M2-macrophage are involved in mesothelioma cancer development. Our data clearly suggest that Treg contributes to mesothelioma and lung cancer developments in different manners that may be due to the immune environments of each cancer developing tissue (lung vs. pleura). Cancer developing frequency and speed may be dependent on the immune environments through Treg-mediated immunosuppression. PD-1/PD-L1 immunotherapy may not be very effective for many mesothelioma patients tested.

T cell, regulatory T cell, M2-macrophage, PD-1, PD-L1

---

**P089: Circulating Biomarkers in Asbestos Exposure and Mesothelioma Before and After Radiation as Part of the SMARTER Protocol**

**Wu L**, **Zaeimi F**, **Sakhuja A**, **Han A**, **Yun H**, **Amjad S**, **Cho J**, **de Perrot M**

1Toronto General Hospital, University Health Network, Toronto, Canada, 2Dept of Radiation Oncology, Princess Margaret Cancer Centre and Toronto General Hospital, University Health Network, University of Toronto, Toronto, Canada, 3Department of Immunology, Faculty of Medicine, University of Toronto, Toronto, Canada

**Poster Session, Virtual, May 7, 2021**

**Results:** To assess anti-tumor immune responses in mesothelioma and lung cancer tumors, we have investigated T cell activation/proliferation in these tumors. Both CD4+ (helper) and CD8+ (cytotoxic) T cell populations were expanded in almost all tumors tested, suggesting that these T cells responded to these cancer cells. Further analysis of T cell activation status also suggests that many of these T cells were memory/exhausted T cells that had lost their direct cancer-killing activities. We subsequently analyzed PD-1-mediated T cell inactivation in these tumors and revealed that PD-1/PD-L1 was not a major immunosuppression mechanism in many of the mesothelioma tumors tested. To investigate how T cell mediated anti-tumor activity was blocked, we further investigated immunosuppressive FOXP3+ regulatory T cell (Treg) and M2-macrophage populations in mesothelioma and lung cancer tumors. Both immunosuppressive cells were increased in mesothelioma tumors. Particularly, Treg populations were increased in a cancer stage-dependent manner in these tumors, suggesting that Treg is strongly involved in mesothelioma cancer development. In contrast, Treg populations were high in Stage1 lung cancer tumors, but were, surprisingly, significantly decreased in Stage2 and Stage3 lung cancer tumors.

**Conclusion:** Both Treg and M2-macrophage are involved in mesothelioma cancer development. Our data clearly suggest that Treg contributes to mesothelioma and lung cancer developments in different manners that may be due to the immune environments of each cancer developing tissue (lung vs. pleura). Cancer developing frequency and speed may be dependent on the immune environments through Treg-mediated immunosuppression. PD-1/PD-L1 immunotherapy may not be very effective for many mesothelioma patients tested.

T cell, regulatory T cell, M2-macrophage, PD-1, PD-L1
The aim of this study was to evaluate serum biomarkers in early stage mesothelioma and determine the impact of a novel treatment protocol - Surgery for Mesothelioma After Radiation Therapy using Extensive pleural Resection (SMARTER) - on serum biomarkers.

**Methods:** The Luminex Multiplex Panel Assay was carried out to quantify the level of 38 cytokines, chemokines and growth factors in the serum of healthy donors without asbestos exposure (HD, n=7), individuals exposed to asbestos but without evidence of mesothelioma (Asb, n=38), and patients diagnosed with malignant pleural mesothelioma (MPM, n=39). MPM were divided into epithelioid and non-epithelioid for comparison. Five MPM patients treated with the SMARTER protocol had blood collected before and after radiation. Gene expression profiling was analyzed by single cell RNA sequencing (scRNA-Seq) from untreated tumor biopsy and pleural effusion from MPM patients. Pathways analysis was then performed using the NetworkAnalyst.ca online.

**Results:** A total of 10 proteins were found to be significantly upregulated (n=5) or downregulated (n=5) in both Asb individuals and MPM patients compared with HD. Upregulated proteins were epidermal growth factor (EGF), MCP-1 (CCL2), sCD40L, Eotaxin (CCL11), and VEGF (VEGFA) (P<0.05), while downregulated proteins were IL-17A, IFN-g, IFN-a2, MIP-1a (CCL3), and MIP-1b (CCL4) (P<0.05). Regulation of endothelial cell proliferation and angiogenesis were the predominantly activated pathways. Although the Th1 cytokine IFN-g was significantly decreased in both epithelioid and non-epithelioid MPM compared to HD, IFN-g level remained significantly higher in epithelioid MPM compared to non-epithelioid MPM. In contrast, Th2 cytokines, IL-4, IL-5, IL-6, IL-9 and IL-13 were significantly higher in non-epithelioid MPM compared to epithelioid MPM. Preoperative radiation as part of SMARTER protocol resulted in significant reduction of the circulating proteins: EGF, VEGF, MCP-1, sCD40L and Eotaxin at the time of surgery, (10±2) days after the end of radiation. scRNA-seq demonstrated that CCL2 and VEGFA were mainly produced by inflammatory monocytes, macrophages and tumor cells, while EGF and CD40L were produced by tumor cells and T cells, respectively.

**Conclusions:** Angiogenic factors and chemokine ligands are upregulated in MPM and down-regulated with a short course of radiation prior to surgery.

Asbestos, Mesothelioma, Luminex, cytokine, chemokine, growth factor

**P090: Comparative Electron Microscope Asbestos Fiber Burden Analysis of Baby Powder in the Bottle and Body**

**Kazan S1, Steinberg H1**

1Kazan Mcclain Satterley Greenwood, Oakland, United States

**Poster Session, Virtual, May 7, 2021**

**Objectives:** That exposure to commercial asbestos causes mesothelioma is well established. But mesothelioma from exposure to asbestos in cosmetic talc/ baby powder is receiving increased attention. Over 119 million consumers in the United States used cosmetic talc in 2019. Evidence demonstrates these users may be exposed to asbestos through the use of talcum baby powder. (Moline, et al. “Mesothelioma Associated with the Use of Cosmetic Talc.” JOEM 2019.) We describe medico-legal lung tissue fiber burden analysis of two adult baby powder users (A and B) with malignant mesothelioma but no exposure to commercial asbestos. Asbestos fibers found in their tissue samples are compared to those found in a popular baby powder brand.

**Methods:** Two adult baby powder users provided detailed personal exposure histories in deposition testimony where the plaintiffs’ and defendants’ counsel explored all potential sources of commercial asbestos exposure, as well as each user’s history of exposure to baby powder. Tissue digestion and fiber burden analysis was performed on tissue from the users’ lung and lymph node tissue via scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The asbestos fibers found in the users were then compared to asbestos fibers historically and contemporaneously found in the baby powder brands the individuals reported using.

**Results:** A review of all evidence presented at both trials demonstrated no alternative sources of commercial asbestos exposure, as well as each user’s history of exposure to baby powder. Tissue digestion and fiber burden analysis was performed on tissue from the users’ lung and lymph node tissue via scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The asbestos fibers found in the users were then compared to asbestos fibers historically and contemporaneously found in the baby powder brands the individuals reported using.

**Conclusions:** Angiogenic factors and chemokine ligands are upregulated in MPM and down-regulated with a short course of radiation prior to surgery.
and lymph tissue. User B’s lymph tissue was examined by tissue digestion and fiber burden TEM analysis. Talc fibers, talc particles, anthophyllite asbestos, tremolite asbestos, and chrysotile asbestos were found in his lymph tissue. A review of historic and contemporary test results of the talcum baby powder at issue reveal matching types of asbestos fibers, talc, and minerals in the baby powder brands they used, including anthophyllite asbestos, tremolite asbestos, and chrysotile asbestos.

**Conclusion:** Only recently have clinicians begun to understand that asbestos-contaminated talc/baby powder presents a risk of potential asbestos exposure. Previously, this potential exposure was unexplored in taking mesothelioma patients’ clinical exposure histories. This may well explain the high incidence of “spontaneous” or “idiopathic” mesotheliomas, especially among women, who appear to be heavier talc users than men. (Finkelstein, “Malignant Mesothelioma and Its Nonasbestos Causes.” Arch. Pathol. Lab. 2019.) The US FDA’s finding of asbestos in baby powder and subsequent recall in October 2019 should increase public and clinical awareness of this potential asbestos exposure source, which should now become a regular part of every mesothelioma patient’s exposure history.

**Keywords:** Asbestos, talc, baby powder, tissue digestion, fiber burden, SEM, TEM

---

**P091: How to Not Find Asbestos Present in Cosmetic Talc in Order to Report “No Asbestos Found”**

**Kazan S**

1Kazan Mcclain Satterley Greenwood, Oakland, United States

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Cosmetic talc is used in thousands of consumer products worldwide, including baby powder. But the methods used by industry to detect asbestos in this talc are designed not to find asbestos fibers that are present, and justify reports saying “no asbestos detected.”

**Methods:** For decades, talc producers and/or product manufacturers have routinely analyzed talc samples for asbestiform mineral content prior to using it in product manufacture. These entities favor an analysis method using X-ray diffraction and a quantifiable detection lower limit of 5 fibers per grid. (J&J Method TM 7024; CTFA Method J 4-1). This information has only recently come to light during litigation of talc mesothelioma cases in the United States.

**Results:** Use of X-ray diffraction (in contrast to TEM’s lower sensitivity limit), has a higher one-percent-by-weight sensitivity limit for asbestos in talc, and cannot distinguish fibrous from non-fibrous material. Where traces of asbestos are present, the asbestos is probably present at less than 1% – not detectable by X-ray diffraction.

The industry’s TEM testing method has a quantifiable detection limit of 5 asbestos fibers per grid; where asbestos fibers are detected below that limit, the sample is reported as “non-quantifiable” asbestos content. This means the technician detected asbestos fibers, but saw less than 5 fibers on review of grid openings. A 22 ounce bottle of baby powder can contain 40,000,000 asbestos structures, to which users will be exposed during regular use, and still be reported as “none detected.”

**Conclusion:** X-ray diffraction scanning of talc is designed to allow a large number of asbestos fibers to go undetected. TEM is the better tool for analysis, as it permits detection of fiber and identification of the actual makeup of fibers. Reports claiming “no quantifiable amounts of asbestiform minerals” based on the standard quantifiable detection limit can actually mean that asbestos fibers were detected, but below the quantifiable detection limit. Talc analyzed under this method for asbestos content has regularly and misleadingly been reported as being asbestos-free, even though it has in fact been the source of significant asbestos exposure for more than 50 years.

**Keywords:** asbestos, talc, baby powder, X-ray diffraction, TEM
P092: Shipbreaking: Creating Accountability
Kazan S1, Meltzer F1
1Kazan Mcclain Satterley Greenwood, Oakland, United States

Poster Session, Virtual, May 7, 2021

Objectives: Ninety percent of shipbreaking in the world is carried out in Bangladesh, China, India, Pakistan and Turkey, an unsustainable, environmentally damaging and deadly industry. Decommissioned ships contain many carcinogenic and toxic substances, with an average ship containing up to 7 tonnes of asbestos. Studies have found an excess mortality in respiratory cancers among shipbreakers. (Wu 2012.) One study found asbestosis in 35% of ship-breakers. (Muralidhar 2017.) Without significant regulatory control, rates of asbestos related diseases including mesothelioma will continue to rise. The east Asian shipbreaking industry is part of the toxic legacy of Western society, and some local victims may be able to pursue legal claims against American companies or the asbestos bankruptcy trusts they established.

Methods: Asbestos is commonly found onboard ships, in boiler and engine rooms, and as insulation on steam pipes ship-wide. Many Western nations have strict regulations on the remediation of asbestos, and ship owners have found it expedient to send ships at the end of their working lives to the developing world for recycling. A ship operates under the laws of its flag state. To save money or to circumvent environmental and safety regulations, vessel owners often register under other flags. Ships beached in East Asian ports for recycling often fly a “flag of convenience”. According to the NGO Shipbreaking Platform the “end-of-life flags” offer special “discount rates” for last voyages and easy short-term registration that bypass regulations restricting movements of hazardous wastes. By using ships registries such as Janes, or MARAD (Vessels of the Maritime Administration vessel history database), one can often determine the origin of the ship, and identify the hazardous materials aboard, allowing a potential remedy for injured workers.

Results: It is common for a ship to change names, registration and ownership many times during its working life. Research into ship history can lead to information regarding its original construction and subsequent repairs. The Vessel Status cards are kept by the Maritime Administration in Washington DC, which is part of the U.S. Department of Transportation. Using MARAD status cards, one can trace the ownership of vessel, from construction through disposal.

Example:
Ship Name: Tirell, completed in Wilmington, North Carolina in 1944
Sold to Pacific Far East lines 1947; renamed California Bear
Renamed American Bear in 1962
Sold to Central Gulf Steamship in 1962, renamed Green Lake
Sold to Oceanic Ore Carriers in 1965, renamed Oceanic Cloud
Sold and scrapped in 1967 to Kuang I Enterprises in China

Conclusion: From fully digitized online sources, it is often possible to track the history of ships from construction to their ultimate end in West Asian shipbreaking yards. This information may help the victims of this unregulated industry achieve justice for the occupational illnesses that result from this deadly form of recycling.

Keywords: shipbreaking, asbestos, remediation, recycling

P093: The Role of Company Doctors in Decisions About Public Health and Product Safety: A Cautionary Tale
Kazan S1, Meltzer F1
1Kazan Mcclain Satterley Greenwood, Oakland, United States

Poster Session, Virtual, May 7, 2021

Objectives: Case Study: The Role of Company Doctors.

“Occupational health professionals must contribute to environmental and community health.”

Robert Wood Johnson recognized this commitment to community well-being when he crafted the Johnson & Johnson Credo in 1943: “The values that guide our decision-making are spelled out in Our Credo. Put simply, Our Credo challenges us to put the needs and well-being of the people we serve first.”

The credo includes these statements:

- Our first responsibility is to the doctors, nurses, hospitals, mothers and all others who use our products.
- Our products must always be of the highest quality.
- We must participate in the promotion of civic improvement—health, education...

A review of internal Johnson & Johnson documents made available through recent litigation reveal that the talc used in baby powder and cosmetic products tested positive for asbestos as early as 1958. This information was concealed from outside medical professionals and the public for over 50 years, during which millions were regularly exposed to asbestos, including untold numbers of babies around the world.

Results: Internal documents show:

In response to an April 9, 1969 internal memorandum from W.H. Ashton asking, “How bad is Tremolite medically, and how much of it can safely be in a talc base?” T.M. Thompson, M.D., J&J’s Associate Director of Clinical Research, responded on April 15, 1969, “On various occasions we have discussed the possibility of carrying out studies on animals which might provide factual information with regard to whether or not variable exposures to talc suspended in the environmental atmosphere might be productive of fibrotic and/or inflammatory reactions in the lungs.

* * * *

“Since pulmonary diseases, including inflammatory, fibroplastic and neoplastic types, appear to be on the increase, it would seem prudent to limit any possible content of Tremolite in our powder formulations to an absolute minimum.”

No sufficient studies were done.

Dr. Thompson also warned that “It is not inconceivable that we could become involved in litigation.”

In a 1974 meeting with the FDA, Johnson & Johnson medical executives claimed, “our very preliminary calculation indicates that substantial asbestos can be allowed safely in a baby powder.” (1/18/1974 Memo to File by Hildick-Smith and W. Nashed)

Johnson & Johnson actively attempted to influence talc studies, commissioned reports on talc safety and hired ghostwriters to submit them to the Journal of Occupational Medicine.

Johnson & Johnson and the Cosmetic, Toiletry, and Fragrance Association (CTFA) trade association sought to influence FDA regulatory terminology, seeking to define talc as containing “no detectable fibrous asbestos minerals” instead of “asbestos-free.”

Conclusion: Despite the admirable scientific prescience of Dr. Thompson, his employer chose to put corporate interests ahead of the public good for decades, putting generations of their customers at risk and likely causing many cases of mesothelioma, past, present, and future.

Keywords: talc, asbestos, Johnson & Johnson

P094: BAP1 Loss is Associated with Higher ASS1 Expression in a Sub-Group of Epithelioid Mesothelioma Suggesting New Therapeutic Options

Barnett S1, Kenyani J1, Querques F1, Goate Z1, Rassl D2, Marciniak S3, Sacco J1, Coulson J1

1University of Liverpool, Liverpool, United Kingdom, 2Royal Papworth Hospital NHS Foundation Trust, Cambridge, United Kingdom, 3University of Cambridge, Cambridge, United kingdom

Poster Session, Virtual, May 7, 2021

Objectives: BAP1 is a deubiquitylase (DUB) that can regulate protein stability and transcription. BAP1 is frequently inactivated by somatic mutation in malignant pleural mesothelioma (MPM), with loss of BAP1 most prevalent in the epithelioid subtype. Moreover, germline BAP1 mutation is linked to a cancer-predisposition
syndrome. To profile changes that occur upon BAP1 loss, we employed multi-omic analyses of an isogenic mesothelial (MeT5A) cell line carrying a cancer-predisposition point mutation (w-; Testa et al. 2011) and promoter trap (KO). One BAP1-dependent candidate that emerged was arginine succinate 1 (ASS1), an enzyme essential for cellular synthesis of arginine and its downstream metabolites. Here we further investigate the relationship between increased ASS1 expression and BAP1-loss in mesothelioma and whether this may be exploited for patient stratification and therapeutic intervention.

Methods: The expression of candidate BAP1-dependencies was validated by immunoblotting and qRT-PCR in the isogenic MeT5A cell lines and assessed in a panel of mesothelioma cell lines of known BAP1 status (13 epithelioid, 6 biphasic, 3 sarcomatoid from MesobanK and ATCC). Co-expression of BAP1 with ASS1 transcript was assessed in the TCGA mesothelioma dataset, and 5 tissue microarrays (TMAs; MesobanK) were stained for BAP1 nuclear expression (a surrogate for BAP1 mutation), cytokeratin (tumour cell marker) and ASS1. Nuclear BAP1 expression was assessed manually by 3 independent observers; total cellular ASS1 protein expression was quantified using QuPath. CellTiter-Glo and Incucyte imaging are being utilised to evaluate the effects of inhibiting ASS1 or its downstream pathways on cell viability.

Results: We confirmed that transcript and protein expression of ASS1 is significantly higher in MeT5Aw-/KO compared to the parental MeT5A+/+ cell line (RNA: Welch’s T-test, p=0.034; Protein: Welch’s T-test, p=0.025) and in MPM cell lines with BAP1 alterations compared to those with normal BAP1 (RNA: Mann-Whitney, p=0.003; Protein: Mann-Whitney, p=0.01). BAP1 and ASS1 mRNA expression is inversely correlated in epithelioid mesothelioma samples (TCGA: Spearman, r=-0.43, p=0.0007) and immunohistochemical staining of mesothelioma TMAs revealed significantly higher ASS1 expression in tumours with (n=55) than without (n=112) nuclear BAP1 expression (Mann-Whitney, p=0.0003). ASS1 tumour H-scores fell into 3 distinct groups low (<80), medium (80-199) and high (≥200), with an increasing proportion of BAP1-negative patients per group. We also observed a trend towards better survival in the sub-group of patients with tumours that were BAP1-negative with high ASS1 expression. Preliminary cell viability assays show that treatment with an ASS1 inhibitor (αMDLA) has a greater effect on proliferation of a BAP1-altered compared to a BAP1-normal cell line.

Conclusion: Our multi-omics analysis pipeline highlighted changes to components involved in a number of cancer-related pathways. BAP1-dependent changes in the metabolic regulator ASS1 were validated in MPM cell lines and patient samples. Although arginine-deprivation shows promise in trials as a therapeutic in ASS1-deficient mesothelioma. Here we confirm that ASS1 can not only be highly expressed in mesothelioma but demonstrate that this is often associated with BAP1-loss. These data may suggest metabolic reprogramming in a subset of BAP1-deficient mesothelioma which could offer alternative therapeutic approaches and supports dual-screening of tumour biopsies for BAP1 and ASS1 expression.

BAP1, ASS1

P095: Identifying Genetic Profiles, Immunological Milieu and Cellular Characteristics Associated with Mesothelioma Susceptibility Using CC-MexTAg Mouse Model

Behrouzfar K1,2, Burton K1,2, Mutsaers S3, Morahan G5, Lake R1,4, Fisher S1,2

1National Centre for Asbestos Related Diseases (NCARD), the University of Western Australia, Perth, Australia, 2School of Biomedical Sciences, the University of Western Australia, Perth, Australia, 3Institute for Respiratory Health, the University of Western Australia, Perth, Australia, 4School of Medicine, the University of Western Australia, Perth, Australia, 5Centre for Diabetes Research, Harry Perkins Institute of Medical Research, Perth, Australia

Poster Session, Virtual, May 7, 2021

Objectives: Mesothelioma is a rare, highly aggressive asbestos related cancer with poor prognosis. Why some people develop mesothelioma, while other people do not, despite the same asbestos exposure history is not clear. Evidence suggests that host genetics may play a role. However, genetic variants identified by conventional genetic studies are often limited to the study cohort due to the relatively small number of mesothelioma patients available for study.
Here we described an expansion of our comprehensive research program involving the Collaborative Cross MexTAg (CC MexTAg) mouse model, designed to elucidate how host genetics affects asbestos related disease (ARD) development (see abstract No#18 Fisher-Collaborative Cross). We have performed comprehensive gene expression and multiplex immunohistological analyses on tumour samples to identify pathways that affect the natural history of the disease with a particular focus on the way the immune response affects survival after diagnosis. Additionally, we have performed a comprehensive analysis of the cellular properties of CC MexTAg derived ascites cell lines. Taken together, these data will be used to improve our understanding on biological pathways associated with ARD progression and susceptibility.

**Methods and aims:**

**Aim1:** Comprehensively profile and compare the acquired genetic mutations in mesotheliomas between protective and sensitive haplotypes and correlate with disease outcome.

We compared differential gene expression profiles and associated signalling pathways in bulk tumour samples between sensitive and protected groups to asbestos related disease using the NanoString™ platform.

**Aim2:** Explore the tumour microenvironment in rapidly progressing mesotheliomas and compare it with indolent disease.

Multiplex immunofluorescence was used to confirm gene expression data and further explore the difference in immunological milieu of mesotheliomas in sensitive and protective mice groups.

**Aim 3:** Describe and compare cellular characteristics of tumour cell lines derived from mesothelioma sensitive and resistant CC MexTAg mice.

We have measured cellular properties such as doubling time, migration rate, cell cycle stage distribution, and immune surface marker expression in different CC MexTAg derived tumour cell lines.

**Results:** We measured cellular characteristics of 22 ascites derived mesothelioma cell lines from 13 high and 9 low survival CC MexTAg groups. Doubling time of cell lines ranged from 23 to 50 hours (median=28) and migration rates ranged from 1.6 to 4.6 relative Wound Density % per hour (median= 2.8) were not correlated with survival rate. However, cell cycle stage distribution (G1 and G2, but not S phase) indicated a weak, but significant correlation with overall survival of CC-MexTAg mice. We next measured the expression of immune surface markers on cell lines before and after IFNy treatment and observed no significant correlation between the changes in the level of immune surface markers with overall survival.

**Conclusion:** Our results indicated that the majority of cellular characteristics of tumour cell lines derived from ascites did not correlate with the 3-fold variation observed of CC-MexTAg mice survival. This suggested further analyses, including assessing genetic profiles and immunological milieu of bulk tumours may yield more useful data that could improve our understanding about the pathobiology of mesothelioma in asbestos exposed CC-MexTAg mice.

Asbestos related disease, CC-MexTAg, Tumour microenvironment, gene expression, cellular characteristics

---

**P096: The Expression of Collagen Receptor uPARAP/Endo180 in Malignant Mesothelioma**

**Cakilikaya P**1, Raagaard Sørensen R2, Behrendt N1, Engelholm L1, Santoni-Rugiu E2,3

1Finsen Laboratory, Rigshospitalet / Biotech Research & Innovation Centre (BRIC), University of Copenhagen, , Denmark, 2Department of Pathology, Rigshospitalet, University of Copenhagen, , Denmark, 3Biotech Research & Innovation Centre (BRIC), University of Copenhagen, , Denmark

**Poster Session, Virtual, May 7, 2021**

Objective: Malignant mesothelioma (MM) is highly aggressive, resistant to therapy, and has limited options for cure. We have previously shown that the endocytic collagen receptor, uPARAP/Endo180, which takes part in extracellular matrix degradation, collagen turnover, and invasion, is upregulated in certain cancers and can be therapeutically targeted. Data-mining for the available mRNA datasets from GEPIA and Oncomine suggested high expression of this receptor in MM. Thus,
we studied the uPARAP/Endo180 protein expression by immunohistochemistry (IHC) in human MM specimens as a first step to evaluate its potential use as a diagnostic marker and therapeutic target.

Methods: The study material consisted of formalin-fixed paraffin-embedded (FFPE) diagnostic biopsies and resections from 12 epithelioid (EMM), 17 biphasic (BMM), and 11 sarcomatoid (SMM) MMs, and 13 non-malignant reactive mesothelial proliferations (RMPs) with fibrosis as controls. We quantified uPARAP/Endo180 expression by H-score; [% of cells stained at intensity 1 (weak) x 1] + [% of cells stained at intensity 2 (moderate) x 2] + [% of cells stained at intensity 3 (strong) x 3] (final score from 0 to 300). uPARAP/Endo180 in MM and other relevant cancer cell lines was assessed by western blotting.

Results: SMM samples showed the highest uPARAP/Endo180 expression within three main subtypes. uPARAP/Endo180 expression was strongly upregulated in all three MM subtypes as compared to RMPs (Fig. 1; p≤ 0.0001, Welch’s ANOVA test), indicating that uPARAP/Endo180 expression correlates with the malignant mesothelial transformation. Furthermore, immunoblotting showed that uPARAP/Endo180 expression levels in MM cell lines were comparable to those in other highly uPARAP/Endo180-positive cancer cell lines.

Conclusion: This study indicates strongly upregulated uPARAP/Endo180 expression in MM. Further validating studies on larger cohorts and functional preclinical models will fully reveal whether this upregulation could be exploited in the diagnostics and therapeutic targeting of MM, as shown for other cancer types.
P097: Heterozygous Germline BLM Mutations Increase Susceptibility to Asbestos and Mesothelioma

Bononi A1, Goto K1,2, Ak G3, Yoshikawa Y4, Emi M1,4, Pastorino S1, Carparelli L1, Ferro A1, Nasu M1, Kim J1, Suarez J1, Xu R1, Tanji M1, Takinishi Y1, Minaai M1, Novelli F1, Pagano I1, Gaudio G1, Pass H4, Groden J6, Grzymski J1, Metintas M1, Akarsu M8, Morrow B9, Hassan R9, Yang H1, Carbone M1

1University of Hawai'i Cancer Center, Thoracic Oncology, Honolulu, United States, 2Hiroshima University, Dept of Urology, Institute of Biomedical & Health Sciences, Hiroshima, Japan, 3Eskisehir Osmangazi University, Lung and Pleural Cancers Research & Clinical Center, Eskisehir, Turkey, 4Hyogo College of Medicine, Department of Genetics, Hyogo, Japan, 5New York University, Department of Cardiovascular Surgery, New York, United States, 6University of Illinois, VC Research, Chicago, United States, 7Desert Research Institute, and Renown Health, Center for Genomic Medicine, Reno, United States, 8Eskisehir City Hospital, Department of Chest Disease, Eskisehir, Turkey, 9National Cancer Institute, Thoracic & GI Malignancies Branch, Center for Cancer Research, Bethesda, United States

Poster Session, Virtual, May 7, 2021

Rare biallelic BLM gene mutations cause the Bloom Syndrome. Whether BLM heterozygous germline mutations (BLM+/-) cause human cancer remains unclear. We sequenced the germline DNA of 155 mesothelioma patients (33 familial and 122 sporadic). We found two deleterious germline BLM+/- mutations within 2/33 families with multiple cases of mesothelioma, one from Turkey (c.569_570del; p.R191Kfs*4) and one from the US (c.968A>G; p.K323R). Some of the relatives who inherited these mutations developed mesothelioma, while none with non-mutated BLM were affected. Furthermore, among 122 patients with sporadic mesothelioma treated at the US-National Cancer Institute, 5 carried pathogenic germline BLM+/- mutations. Therefore, 7/155 unrelated mesothelioma patients carried BLM+/- mutations, significantly higher (P = 6.7E-10) than the expected frequency in a healthy, unrelated population from the gnomAD db, and 2/7 carried the same missense pathogenic mutation c.968A>G, (P = 0.0017, given a 0.00038 mutation probability). Experiments in primary mesothelial cells from Blm+/- mice, and in primary human mesothelial cells in which we silenced BLM, revealed that reduced BLM levels promote genomic instability while protecting from cell death, and promoted TNF-α release. Blm+/- mice injected intraperitoneally with asbestos had higher levels of pro-inflammatory M1 macrophages, and of TNF-α, IL-1β, IL-3, IL-10, IL-12 in the peritoneal lavage, findings linked to asbestos carcinogenesis. Blm+/- mice exposed to asbestos had a significantly shorter survival and higher incidence of mesothelioma, compared to controls. We propose that germline BLM+/- mutations increase the susceptibility to asbestos carcinogenesis enhancing the risk of developing mesothelioma.

mesothelioma, gene-environment, genetics, BLM, asbestos

P098: Overcoming Resistance to Arginine Deprivation Therapy in Malignant Pleural Mesothelioma

Carpentier J1, Szlosarek P1, Martin S1

1Barts Cancer Institute, London, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: Malignant Pleural Mesothelioma (MPM) remains an asbestos-related disease associated with poor prognosis. Previous reports have shown that 50% of MPM are deficient in the arginine synthesis gene, Argininosuccinate Synthetase 1 (ASS1). A therapeutic strategy involving arginine deprivation is a promising way of treating these MPM patients. Without ASS1 expression, cells are dependent on extracellular arginine and cannot survive without external arginine. ADI-PEG20 is an arginine deprivation compound presently tested in several clinical trials for the treatment of ASS1-deficient cancers. However, ASS1-deficient MPM patients can develop resistance to this therapy, it is important to understand resistance mechanisms to prevent resistance and identify new ways of treating ADI-PEG20-resistant diseases. Our previous results have shown that ADI-PEG20-resistant cells have a deregulated polyamine metabolic pathway, which can be targeted therapeutically. We are now investigating whether combinatory treatment composed
of ADI PEG20 and polyamine inhibitors constitute a promising novel therapeutic strategy to overcome ADI-PEG20 resistance in MPM patients.

**Methods:** To generate ADI-PEG20-resistant cell models, epithelial and biphasic MPM cell lines were treated with an increasing concentration of ADI-PEG20 over time. After approximately 6 months, resistant cells were generated in both Ju77 (epithelial) and MSTO (biphasic) cell lines. Protein expression analysis and metabolomics were performed to identify differences between ADI-PEG20 resistant and sensitive cell lines. Different polyamine inhibitors were assessed to study their potential for a combinatorial treatment with ADI-PEG20.

**Results:** New models of resistance to ADI-PEG20 therapy for MPM were generated, one derived from an epithelial MPM form (Ju77R) and one derived from a biphasic MPM form (MSTOR). Our results suggested that resistance was linked to ASS1 re-expression via the demethylation of the ASS1 promoter. ASS1 mRNA level increased by 50 fold in the Ju77R cells and by 1000 fold in the MSTOR cells. Metabolomics analysis revealed that polyamine metabolism was rewired in these cells upon resistance to ADI-PEG20 with an increase of the level of acetylated polyamines suggesting an increase of polyamine catabolism and decrease of polyamines levels upon ADI-PEG20 treatment. Treatment of ADI-PEG20 resistant cell lines with a range of different polyamine inhibitors demonstrated that ADI-PEG20 resistance cell lines were sensitive to the spermidine-analog GC7. Therefore suggesting that combinatorial treatment of GC7 with ADI-PEG20 may eliminate the emergence of resistance upon ADI-PEG20 treatment.

**Conclusion:** We have generated a range of novel cellular models of resistance to ADI-PEG20 which helped to elucidate mechanisms of ADI-PEG20 resistance and assessed the therapeutic potential of combinatorial treatments of ADI-PEG20 with GC7.

ASS1, Polyamine, ADI-PEG20, GC7, Drug Resistance, Metabolism, Arginine, Cell Models
P099: Butyrate Sensitizes Epithelioid Mesothelioma Cells to Oxaliplatin

Chen J1, Vitetta L1,2, Hall S1

1Medlab Clinical Ltd, Alexandria, Australia, 2The University of Sydney, Faculty of Medicine and Health, Camperdown, 2050

Poster Session, Virtual, May 7, 2021

Objectives: Mesothelioma is difficult to cure due to the resistance to chemotherapeutic agents. Butyrate, a metabolite elaborated by gut commensal bacteria, exerts anti-cancer effects through inhibition of multiple oncogenic signalling pathways. However, it has not been tested as to whether butyrate could increase the therapeutic efficacy of chemotherapeutic agents for the treatment of mesothelioma. The aim of this study was to examine the combination effect of butyrate and the chemotherapeutic agent oxaliplatin on pleural mesothelioma cells.

Methods: H2452 epithelioid mesothelioma cells, which were primarily isolated from a male mesothelioma patient, were cultured in RPMI-1640 medium containing 10% calf serum. These cells were seeded in 96-well plates and treated with oxaliplatin in the concentrations of 25μg/ml, 50μg/ml, 100μg/ml and 200μg/ml and butyrate at concentrations of 1.25mM, 2.5mM, 5mM and 10 mM in serum-free medium with various time durations. The cells were also treated by the combination of oxaliplatin and butyrate. In addition, butyrate was used to treat H2452 cells stimulated with 1%, 5% and 10% calf serum. Cytotoxicity was examined by resozurin assay and morphological changes were observed under inverted microscope.

Results: Both butyrate and oxaliplatin produced dose- and time-dependent cytotoxicity on the H2452 mesothelioma cells. Addition of butyrate sensitized mesothelioma cells to oxaliplatin treatment. The combination effect of butyrate and oxaliplatin is shown below. Data represent three independent experiments (Table 1).

Sodium butyrate also markedly increased the damage of mesothelioma cells by oxaliplatin morphologically.

The effect of butyrate was also examined in different concentrations of calf serum-promoted growth of mesothelioma cells for 5 days. Data are from three independent experiments performed in different days. The results obtained revealed that calf serum increased mesothelioma cell growth in a dose-dependent manner. The control was the values of cells cultured in serum free medium. The values from the controls were set as 100% for comparison of other values. Addition of 1%, 5% and 10% calf serum increased cell viabilities to 128±11%, 197±24% and 219±26% of control respectively. Butyrate at 2mM significantly reduced cell viabilities into 45±12%, 49±4%, 69±12% and 96±32% respectively. Addition of butyrate also caused morphological changes observed under inverted microscope.

Conclusions: Butyrate increases the sensitivity of mesothelioma cells to oxaliplatin treatment. Calf serum increases mesothelioma cell growth in a dose-dependent fashion, which can be overcome by butyrate.

Butyrate, Oxaliplatin, H2452, Cytotoxicity
P100: Immunomodulatory Activity of Epigenetic Drugs Combinations in Mesothelioma: Laying the Ground for New Immunotherapeutic Strategies

Cannito S1, Chiarucci C1, Cutaia O1, Fazio C1, Lofiego M1, Piazzini F1, Solmonese L1, Calabrò L1, Coral S1, Maio M1, Covre A1

1Center for Immuno-Oncology, Department of Oncology, University Hospital of Siena, Siena, Italy

Poster Session, Virtual, May 7, 2021

Objectives: Growing evidence are demonstrating the efficacy of immune check-point inhibitors (ICI) therapy in mesothelioma patients; however, a limited percentage of patients benefits from this therapeutic approach yet, and a better understanding of mesothelioma immunobiology will likely contribute the efficacy of ICI therapy. In this scenario, epigenetic modifications occurring during mesothelioma progression may play a relevant role in negatively regulating the cross-talk between tumor cells and the immune system, as well as contributing to the highly immunosuppressive microenvironment of mesothelioma. Therefore, a better understanding of the epigenetic landscape of mesothelioma could open the path to novel and potentially more effective immunotherapeutic approaches combining ICI and epigenetic drugs. In this study we investigated the immunomodulatory potential of diverse epigenetic agents by comparing the activity of DNA hypomethylating agents (DHA) with histone deacetylases inhibitors (HDACi) and EZH2 inhibitors (EZH2i), alone or combined with DHA, in mesothelioma cells.

Methods: Mesothelioma cell lines (#2 sarcomatoid, #1 biphasic, #1 epithelioid) were treated with the DHA guadecitabine 1μM, or with the HDACi, Valproic Acid (VPA) 1mM, or the EZH2i, EPZ-6438 1μM, alone or combined with guadecitabine. We investigated expression of HLA class I molecules by flow-cytometry and of immune checkpoint molecules (i.e., PD-L1), cancer testis antigens (CTA, i.e., NY-ESO, MAGE-A1), Natural Killer Group 2 member D Ligands (NKG2DLs, i.e., MIC-A, MIC-B, ULBP2) and EMT-regulating cadherins (i.e., CDH1, CDH2) by quantitative Real-Time PCR. Fold change (FC) expression was calculated for each treatment vs untreated cells and reported as mean values of FC (FCm) among investigated mesothelioma cell lines. A positive modulation of the expression was considered if FC/FCm>1.5.

Results: Heterogeneous immunomodulatory effects were observed in investigated mesothelioma cell lines treated with epigenetic drugs alone. In detail, guadecitabine upregulated the expression of all immune-molecules, HLA class I antigens (FCm=1.75), PD-L1 (FCm=2.38), NKG2DLs (MIC-A FCm=1.96, MIC-B FCm=2.57, and ULBP2 FCm=3.56), and upregulated/induced CTA expression. Similarly, VPA upregulated HLA class I antigens (FCm=1.67), PD-L1 (FCm=3.17), NKG2DLs (MIC-A FCm=1.78, MIC-B FCm=3.04, and ULBP2 FCm=3.75) expression; however, CTA expression was modulated only in 1 mesothelioma cell line. Conversely, EPZ-6438 induced minimal immunomodulatory effects by up-regulating only NY-ESO-1 and MIC-B expression in 1 mesothelioma cell line.

Despite the heterogeneous activities of single epigenetic drugs, the addition of both VPA and EPZ-6483 to guadecitabine strengthened the immunomodulatory effects of the latter in mesothelioma cells, by affecting the expression of all investigated molecules. Specifically, guadecitabine plus VPA or EPZ-6438 upregulated the expression of HLA class I antigens FCm=2.55 or 2.69, PD-L1 FCm=8.04 or 2.65, MIC-A FCm=3.81 or 2.26, MIC-B FCm=8.00 or 3.03, ULBP2 FCm=6.24 or 4.53, in mesothelioma cells, respectively. Lastly, higher levels of upregulated/induced CTA expression were observed after both combination treatments vs guadecitabine alone.

Cadherins modulation was mesothelioma histotype-related: CDH1 expression was induced in the 2 constitutive-negative sarcomatoid mesothelioma cells by guadecitabine alone or combined with VPA or EPZ-6438; CDH2 expression was upregulated by VPA alone (FCm=1.50) or plus guadecitabine (FCm=2.54).

Conclusion: Combination of DHA-based immunotherapies with other classes of epigenetic drugs could be an effective strategy to be pursued in mesothelioma clinic.

Keywords: Epigenetics, DHA, HDACi, EZH2i
**P101: Loss of a Single Copy of the Tumour Suppressor Gene NF2/Merlin Does Not Accelerate Pleural Disease Induced by Long-Fibre Carbon Nanotubes or Asbestos**

Crixtom A1, Galavotti S1, Chernova T1, Zarcas-Cabanas J1, Sun X1, Ficken P2, Donaldson K2, Poland C1, Willis A1, MacFarlane M1

1MRC Toxicology Unit, University of Cambridge, Leicester, United Kingdom, 2Department of Cancer Studies, University of Leicester, Leicester, United Kingdom, 3MRC, Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant mesothelioma is associated with exposure to asbestos fibres. It has poor prognosis due to its frequent diagnosis at advanced disease stage and its refractory nature to current therapies. Chronic inflammation induced by retention of pathogenic asbestos fibres in the pleural cavity, in a length-dependent manner, plays an important role in tumorigenesis. Engineered long carbon nanotubes (LNT), which have a high-aspect ratio like asbestos fibres (LFA), likely present a comparable inhalation hazard. The molecular mechanisms by which they promote inflammatory disease and in some cases, sporadic mesothelioma, remain comparatively unexplored.

The tumour suppressor neurofibromatosis type gene 2 (NF2/merlin) is one of the most frequently mutated and/or deleted genes in malignant mesothelioma. It encodes merlin, a protein most closely related to the ezrin-radixin-moesin family proteins, which localises at cell-surface structures to facilitate interaction between plasma membranes and actin filaments.

In this study, our aim was to test whether loss of a single copy of NF2/Merlin enhances inflammatory/fibrotic respiratory disease in mice upon exposure to occupationally-relevant doses of LNT and/or LFA.

**Methods:** C57BL/6 WT or NF2+/- female mice (30 per group) were intrapleurally injected with occupationally-relevant doses of 2 x 0.1μg LNT or 25 μg LFA. Mice were monitored twice daily for up to 20 months. Following onset of symptoms of respiratory disease, mice were humanely killed under Schedule 1 and mesothelioma tissue (encompassing chest wall, diaphragm and heart) processed for histology.

**Results:** Using a model of direct injection of LNT or LFA into the pleural cavity, the site of mesothelioma development, we performed a hazard mechanism study to investigate the incidence of pleural disease encompassing chronic inflammation and/or fibrotic lesions in wild-type (WT) and NF2 heterozygous mice. Surprisingly, our results show that loss of one copy of NF2 does not accelerate and/or enhance the incidence of LNT or LFA-induced inflammatory and/or fibrotic disease following pleural exposure. Exposure to LNT or LFA induced a common molecular signature characterised by chronic activation of key signalling pathways in the pleurae, including Src-family kinases. Pleural effusion-derived cell lines from LNT- and LFA-injected mice displayed characteristic molecular hallmarks observed in human mesothelioma cases, including loss of CDKN2A (encoding p16, p19) and NF2. Additional studies investigating the immune cell landscape of the fibrotic/inflammatory lesions are currently underway.

**Conclusion:** Loss of a single copy of NF2/Merlin does not accelerate or enhance the incidence of inflammatory/fibrotic respiratory disease following intrapleural injection of occupationally-relevant doses of long carbon nanotube fibres or asbestos.

**Keywords:** μ

**P102: Gemcitabine Elicits Enhanced T- and NK-cell-activation in Peripheral Blood of Malignant Mesothelioma Patients: Results from an Open Label Phase II Multicenter Trial (NVALT19)**

de Gooijer C1, Dammeijer F2, van Gulijk M2, Platte E1, Lucas M1, Jebbink M1, Cornelissen R2, Geraerds E3, Barlo N4, Biesma B5, Stigt J6, Bootsma G7, Pitz C8, van den Borne B9, Pronk N10, van Walree N11, van der Noort V1, Aerts J2, Burgers J1

1Netherlands Cancer Institute, Amsterdam, The Netherlands, 2Erasmus University Medical Center, Rotterdam, The Netherlands, 3Groene Hart Hospital,
**Objectives:** Platinum-pemetrexed combination chemotherapy is the first-line treatment for malignant mesothelioma. However, eventually all patients develop progressive disease with prognosis remaining poor. We have recently shown that -switch maintenance therapy- using gemcitabine significantly prolonged the time to progression after first line therapy in mesothelioma patients. It was previously reported that gemcitabine might have immune-modulatory effects. In light of recent trials showing limited efficacy of PD-1-blocking antibodies in mesothelioma, rational and effective combination therapies are warranted to improve patient survival. An improved insight into the immune-modulatory effect of gemcitabine may provide a scientific rationale guiding further combination therapy development in mesothelioma and identify potential biomarkers of treatment response.

**Methods:** Peripheral blood mononuclear cells (PBMCs) were collected from the NVALT19 trial, which was a randomized open label phase II trial comparing switch maintenance gemcitabine with best supportive care (BSC) in 130 malignant mesothelioma patient who did not progress after first line chemotherapy. In order to assess the immune-modulatory properties of gemcitabine we performed comprehensive multi-color flow cytometry on PBMCs from patients on baseline and three weeks following start of chemotherapy.

**Results:** Matched pre- and post-treatment PBMCs, 24 paired samples, including both MDSCs and PBMCs, were included. In patients treated with gemcitabine, an effect on T- and NK-cell proliferation and immune-activation in peripheral blood was found, as evidenced by significantly increased Ki-67 positivity and increased expression of T- and NK-cell co-stimulatory molecules including ICOS, CD28 and HLA-DR. T-regulatory cell proliferation, on the other hand, was strongly decreased following gemcitabine treatment, indicating preferential immune modulatory effects of this drug. Furthermore, the aforementioned changes in immune cell phenotype did not occur in BSC-patients who rather displayed a decrease in NK- and CD8+ T-cell proliferation through time. In addition, whereas CTLA-4 expression was consistently decreased in both treatment arms, albeit much more profoundly following chemotherapy, PD-1 expression was increased on CD4+ and CD8+ T cells only in gemcitabine-treated patients. Although analyses were explorative, we found that an increase in NK-cell proliferation and an increase in PD-1-expression on proliferating (but not total) CD8+ T cells was associated with improved clinical outcome following gemcitabine.

**Conclusion:** Besides prolonging progression free survival in mesothelioma patients, gemcitabine had a widespread effects on circulating immune cells of mesothelioma patients with responding patients displaying increased NK-cell and PD-1 + T-cell proliferation. Further studies are warranted to investigate the direct immunomodulatory effects of gemcitabine or indirect effects through immunogenic cell death.

**Keywords:** Gemcitabine, modulated T- and NK-cell, immunity, PD-1, CTLA-4

---

**P103: Transglutaminase Serves as a Mesothelioma Cancer Stem Cell Survival Factor and Therapy Target**

**Eckert R1, Adhikary G1, Grun D1, Alexander H2, Friedberg J1, Xu W1, Keillor J3, Kandasamy S2**

1University Of Maryland School Of Medicine, Baltimore, United States, 2Rutgers Robert Wood Johnson Medical School, New Brunswick, United States, 3University of Ottawa, Ottawa, Canada

**Objectives:** Mesothelioma is a rare cancer of the mesothelial cell lining of the pleura and peritoneum that is typically caused by asbestos exposure and is highly aggressive and therapy resistant. For this reason, new therapy strategies for treating this cancer must be identified. Cancer stem cells comprise a highly aggressive subpopulation of slow replicating cells that often mediate tumor drug resistance. Our goal is to identify new proteins that drive mesothelioma cancer stem cell (MCS cell).
survival and to assess their potential as therapy targets.

**Methods:** Transglutaminase 2 (TG2) is an important cancer stem cell survival protein that we have identified as highly elevated in MCS cells. In the present paper, we use cell culture, tumor formation and biochemical methods to examine the role of TG2 in driving the MCS cell phenotype and tumor formation.

**Results:** We show that TG2 is highly expressed in human mesothelioma tumors and in MCS cells. TG2 knockdown or TG2 inhibitor treatment reduces MCS cell spheroid formation, matrigel invasion, migration and tumor formation. Moreover, time to tumor first appearance is greatly extended in TG2 knockout cells as compared to wild-type cells. In addition, TG2 loss is associated with reduced expression of stemness, and epithelial mesenchymal transition markers, and enhanced apoptosis.

**Conclusion:** These studies show that TG2 is a key MCS cell survival protein and that TG2 is required for tumor formation. Moreover, we show that a novel TG2-selective inhibitor (NC9) suppresses the MCS cell phenotype and markedly reduces tumor formation. These findings suggest that TG2 serves as a MCS cell survival factor and that it may be a viable therapy target in mesothelioma.

**Keywords:** mesothelioma, transglutaminase, TGM2, stem cell, EMT, apoptosis, NC9, tumor progression

**P104: Endogenous Retrovirus Expression Activates Type-I Interferon Signaling in an Experimental Mouse Model of Mesothelioma Development**

Sun S¹, Frontini F¹, Qi W², Hariharan A¹, Ronner M¹, Wipplinger M¹, Blanquart C³, Rehrauer H², Fonteneau J³, Felley-Bosco E¹

¹University Hospital Zurich, Zurich, Switzerland, ²Functional Genomics Center Zurich, Zurich, Switzerland, ³CRCINA, INSERM UMR 1232, Nantes, France

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Early events in an experimental model of mesothelioma development include increased levels of RNA editing by adenosine deaminase acting on double-stranded RNA (dsRNA). We made the hypothesis that expression of endogenous retroviruses (ERV) contributes to dsRNA formation and type 1 interferon (IFN) signaling.

**Methods:** ERV and IFN-induced genes (ISGs) expression was determined in RNA-seq data from tissues in three groups of mice: sham and asbestos exposed mice with or without tumors. ERV and ISGs expression was confirmed by qPCR. Methylation of genomic DNA was assessed after treatment with sodium bisulfite followed by quantitative methylation specific PCR. DNA demethylation was induced in mouse embryonic fibroblasts (MEF) and mesothelioma cells by 5-Aza-2'-deoxycytidine (5-Aza-CdR) treatment. dsRNA was quantified by flow-cytometry. Activation of IFN signalling was document by gene expression and Western blot (phospho-Irf3, phospho-Stat1, ISG). Sensors of dsRNA were identified by silencing Mavs, Rig-I and Mda5. To block the type-I IFN signaling, cells were treated with Ruxolitinib or anti-IFNAR1 antibodies.

**Results:** ERV and ISGs expression were significantly higher in tumor compared to non-tumor samples. 12 tumor specific ERV were identified and verified by qPCR in mouse tissues. “MesoERV1-12” expression was lower in mouse embryonic fibroblasts (MEF) compared to mesothelioma cells. “MesoERV1-12” levels were significantly increased by demethylating agent 5-Aza-CdR treatment and were accompanied by increased levels of dsRNA, Irf3 activation and ISGs. Basal ISGs expression was higher in mesothelioma cells compared to MEF. It was decreased by silencing Mavs and Mda5, treatment with JAK inhibitor Ruxolitinib or anti-Ifnar1 antibodies. “MesoERV7” promoter was demethylated in tissue from asbestos exposed compared to sham mice and in mesothelioma cells and MEF upon 5-Aza-CdR treatment.

**Conclusions:** These observations uncover novel aspects of asbestos-induced mesothelioma whereby ERV expression increases due to promoter demethylation and is paralleled by increased levels of dsRNA and activation of type-I IFN signaling. These features are important for early diagnosis and therapy.

Asbestos; RNA editing; endogenous retroviruses; type 1 interferon
P105: Contribution of RNA Editing to Mesothelioma Heterogeneity

Felley-Bosco E1, Fonteneau J2, Qi W3, Ronner M1, Hariharan A1, Blanquart C2, Rehrauer H3

1Laboratory Of Molecular Oncology, Dept Thoracic Surgery, USZ, Zurich, Switzerland, 2CRCINA, INSERM UMR 1232, Nantes, France, 3Functional Genomics Center Zurich, ETH Zurich, University of Zurich, Zurich, Switzerland

Poster Session, Virtual, May 7, 2021

Objectives: Recent studies have shown heterogeneity of genetic alterations and transcription profile in mesothelioma. In an experimental model of mesothelioma development in Nf2+/- mice exposed to asbestos (crocidolite) we have observed increased levels of A -> G mutations of RNA in pre-cancer lesions which were maintained in tumors (Rehrauer, Wu, et al., Oncogene, 2018). These changes result from the activity of adenosine deaminases acting on dsRNA (Adar1 and Adar2). One isoform of Adar1 is induced by interferon type 1, which is generally associated to anti-viral response. Our aim was to investigate how RNA editing contributes to mesothelioma heterogeneity.

Methods: RNA editing levels in human mesothelioma were determined with the Alu editing index (AEI) computational tool using Mesothelioma TCGA RNA-seq data. Additional data were obtained using either primary mesothelioma cells or mesothelioma cell lines. When RNA-seq data was not available, AZIN1 editing levels using RNA editing site-specific qPCR (RESS-qPCR) was used as surrogate. Levels of RNA editing were correlated to ADAR1 and ADAR 2 expression levels. Basal type 1 interferon signalling was based on expression of interferon-induced genes (ISG).

Results: ADAR activity is heterogenous in mesothelioma and editing of some regions depends on BAP1, a tumor suppressor gene frequently mutated in mesothelioma. This is relevant since activation of type 1 interferon signaling has been observed in tumors with BAP1 inactivation (Hmeliak, Sanchez-vega et al, Cancer Discovery 2018). Levels of A-to-G mutations in RNA are correlated to the expression of ADAR1 in TCGA mesothelioma data, primary mesothelioma cultures and mesothelioma cell lines. We have also observed that primary mesothelioma cultures that are sensitive to Measle oncolytic viruses and which have an intact IFNB1 gene show a basal activation of type 1 interferon pathway and have an increased ADAR activity.

Conclusion: Overall, our analysis confirm that RNA mutations contribute to mesothelioma heterogeneity and suggest that ADAR activity is relevant in the context of immunotherapies.

Keywords: Mesothelioma, Asbestos, RNA editing, BAP1, type 1 interferon

P106: Results of the Meso-ORIGINS Feasibility Study and An Update on the PREDICT-Meso Accelerator Network

Ferguson K1, Mercer R1, King J3, Marshall K3, Welch H3, Tsim S1, Maskell N1, Evison M5, Rahman N4, Blyth K1,2

1Glasgow Pleural Disease Unit, Queen Elizabeth University Hospital, Glasgow, United Kingdom, 2Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, United Kingdom, 3Academic Respiratory Unit, University of Bristol, Bristol, United Kingdom, 4Oxford Respiratory Trials Unit, Oxford, United Kingdom, 5University Hospital of South Manchester, Manchester, United Kingdom

Poster Session, Virtual, May 7, 2021

OBJECTIVES: Malignant Pleural Mesothelioma (MPM) is typically preceded by chronic pleural inflammation, and frequently by overt pleural effusion. In such cases pleural biopsy may be performed on suspicion of MPM but reveals only benign pleuritis. However, MPM subsequently evolves in an estimated 5-15% of cases, providing a unique window of opportunity for translational research. In the PREDICT-Meso international accelerator network (funded by CRUK/AIRC/FAECC) we will recruit a large cohort of patients with initial benign pleural biopsies to a detailed surveillance protocol. We will collect repeat biopsies in the minority who evolve into MPM and use the Benign-MPM tissue pairs generated to define key biological events in MPM carcinogenesis. We will also generate a suite of pre-clinical models and perform high-throughput drug screening and target-drug validation. The current feasibility study addressed the technical feasibility, patient acceptability and sample size needed for this prospective, multi-centre study, called Meso-ORIGINS.
METHODS: The study was conducted in 4 UK pleural disease centres (Glasgow, Manchester, Oxford, Bristol) between January 2019 & January 2020. The primary objective was recruitment feasibility, defined by prospective recruitment of ≥27 eligible patients over 12-months, using the following criteria: 1) asbestos exposure 2) histological or radiological (e.g. pleural plaques) evidence of benign pleural inflammation. In this arm, the technical feasibility of repeat biopsy (by thoracoscopy or ultrasound (US) cutting biopsy) was also assessed after 6 months. The acceptability of various surveillance strategies (blood, breath tests, imaging, effusion sampling, re-biopsy) was also assessed by questionnaire. The secondary objective was to determine the sample size needed to generate at least 63 Benign-MPM tissue pairs for downstream PREDICT-Meso pipelines. This was assessed in a retrospective analysis of pathology databases and electronic records using similar eligibility criteria. MPM evolution was defined by any subsequent diagnosis within 2-years of initial benign biopsy.

RESULTS: 37 eligible patients were recruited to the prospective element of the study. 27/37 had repeat biopsy feasibility assessed per protocol (9 could not attend due to COVID, 1 patient died < 6 months). Re-biopsy by thoracoscopy or US was feasible in 16/27 (59%; thoracoscopy 13/27 (48%), US 3/27 (11%)). However, re-biopsy was not always acceptable when feasible (e.g. 5/13 patients would not consent to thoracoscopy which was feasible). 257 eligible patients were selected for the retrospective database analysis. Mean (SD) age was 72(9) years. 95% of cases were male. 26% had features suggestive of pleural malignancy on baseline CT. MPM evolution was confirmed histologically in 36/257 (14% (95%CI 10.5-19.2)) during 2-year follow-up. Although not an a priori objective, MPM evolution was also observed in 4/37 (10.8%) cases in the prospective arm during 6-month follow up.

CONCLUSION: The MPM evolution rate observed in the large retrospective analysis (14% (95%CI 10.5-19.2)) suggests 450 benign patients will be required to generate ≥63 Benign-MPM tissue pairs. This sample size is feasible when upscaled over the planned 41-month recruitment period and a large UK pleural disease network. The surveillance protocol deployed will need to include a range of re-biopsy techniques and non-invasive methods. Meso-ORIGINS will open in Q3/4 2021.

Keywords: Mesothelioma, Benign asbestos pleural effusion, BAPE, thoracoscopy, asbestos, pleuritis

P107: Mouse Models of Mesothelioma: Unique Resources for Pre-clinical and Co-clinical Studies


1National Centre for Abestos Related Diseases (NCARD), Perth, Australia, 2School of Biomedical Sciences, The University of Western Australia, Perth, Australia, 3School of Medicine, The University of Western Australia, Perth, Australia, 4Institute for Respiratory Health, Perth, Australia, 5Telethon Kids Institute, Perth, Australia, 6Anatomical Pathology, PathWest Laboratory Medicine, Perth, Australia, 7Canada’s Michael Smith Genome Sciences Centre, Vancouver, Canada, 8Centre for Diabetes Research. Harry Perkins Institute of Medical Research, Perth, Australia

Objectives: One unusual feature of mesothelioma is that the carcinogen, asbestos, induces a similar tumour in both mice and humans; which makes it rare in the field of cancer research and presents an ideal opportunity to apply small animal models to advance mesothelioma research. Since 1992, researches from the National Centre for Asbestos Related Disease (NCARD) have generated an extensive suite of well-characterised cell lines and animal models that reliably recapitulate many features of human mesothelioma. Together, with our biobank of donated patient samples (PP01.05), we have utilised these models to facilitate research aimed at improving the diagnosis and treatment of asbestos related disease, as well as the development of early intervention strategies to reduce disease burden. Here we summarise our collection of models and our endeavours to develop new models to examine their application to pre-, and co clinical mesothelioma research.

The objective is to generate and use asbestos induced murine mesothelioma cell lines, transfectants and transgenic mice as informative models for the preclinical study of mesothelioma.

Methods: Cell lines were established from ascites that developed after intraperitoneal (i.p.) injection of crocidolite asbestos into BALB/c, C57Bl6 and CBA mice.
and characterised, including in vivo growth following subcutaneous (s.c.), i.p. and intrapleural (i.pl) injection. Selected lines have been stably transfected to express a variety of genes including cytokines (IL2/12 and others), alloMHC genes, costimulatory molecules, antigens (e.g. HA and OVA) and various reporter molecules.

Further characterisation has included whole exome sequencing, RNAseq, immunology, immunotherapy using a variety of agents (e.g. α-CTLA4, α-CD40, α-PD1, α-OX40, α-GITR, TLR agonists, and others), surgery (e.g. effects of debulking), neo-antigens (mutation-derived), systems biology, chemotherapy (ex vivo and in vivo), T cell receptors and biology (e.g. role of matrix). As in humans, asbestos related disease (ARD) occurs infrequently in mice. However, ARD occurs reliably, predictably and with high incidence in asbestos exposed MexTAg transgenic mice. Unlike other transgenic models, MexTAg mice require the relevant carcinogen, asbestos, for mesothelioma development and develop few, if any, non asbestos related cancers. Recently we combined our MexTAg mouse model with the Collaborative Cross (a mouse genomic resource) to rapidly identify genes associated with hereditary predisposition to asbestos induced mesothelioma development (PL01.05).

Results: To date, these pre-clinical cell lines and models have been used in 80+ mesothelioma publications and the data generated has, and continues to inform our clinical trial programs. Our endeavour to redevelop, refine and repurpose these models for diverse research programs from identifying mutated neo-antigens through to defining immune gene expression networks, TCR diversity and assessing responses to novel treatments is highlighted by the many abstracts presented at IMIG 2020 (Abstracts: PL01.05, PL04.06, MS03.05, MS07.04, MS15.05, PP05.03, PP05.05, PP05.07, PP05.10, PP08.03, PP08.14, PP08.29).

Conclusion: These NCARD murine models of mesothelioma represent some of the most powerful preclinical tools for the evaluation of the biology, immunology and therapy of mesothelioma available to the research community and their use has led, and continues to lead, to new therapeutic approaches.

Keywords: mouse models, mesothelioma, asbestos, MexTAg, immunotherapy, surgery, chemotherapy, radiotherapy, sequencing

P108: Bioinformatic Analysis of Chromosomal Alterations in Malignant Pleural Mesothelioma

Freyaldenhoven S1, De Rienzo A1, Severson D1, Richards W1, Bueno R1

1Brigham And Women’s Hospital, Division of Thoracic Surgery, Boston, United States

Poster Session, Virtual, May 7, 2021

Objectives: Malignant pleural mesothelioma (MPM) is characterized by complex genetic alterations identified by karyotypic studies and molecular analyses in tumor specimens and cell lines. However, no specific aberrations for diagnostic and differential purposes has been identified. The objectives of this study were to explore patterns of alterations involving whole chromosome (WCA) in MPM and correlate them to clinicopathologic data and gene expression signatures.

Methods: Single nucleotide polymorphism (SNP) data from 95 MPM paired tumor-normal samples (BWH cohort) were available in the laboratory from a previous study (Bueno, 2016). In addition, data from 87 paired MPM samples (TCGA cohort) were obtained through The Cancer Genome Atlas (TCGA). Chromosomal copy number alteration (CNA) analysis was performed using GISTIC. Alterations in which both arms of a chromosome had > 50% of the genes effected (i.e. both arms showing chromosomal loss or both showing chromosomal gain) were classified as WCAs. The overall WCA burden was assigned to each tumor by the total number of WCAs observed in each sample. Samples were stratified into two groups (low and high) by WCA burden using the bottom quartile as a cutoff. Potential association with clinical characteristic were investigated. Overall survival (OS) was estimated by the Kaplan–Meier method. Pathway analysis was performed using Gene Set Enrichment Analysis (GSEA) and a False Discovery Rate ≤ 1x10^-5.

Results: The sum of the number of chromosomal WCA was estimated for each tumor. The median number of WCA burden in each tumor was 3 in both BWH and TCGA cohorts as well as in the overall cohort. The WCA burden positively correlated with other genomic alterations including percent of the genome with copy number alterations (r = 0.42; p < 0.001) and total number of mutations (r = 0.003; p =0.003). Low WCA burden was
significantly associated with improved survival in both cohorts (log-rank; BWH: p=0.005; TCGA: p = 0.009), as well as in the entire cohort (p=0.00014). WCA burden remained significant in multivariate Cox hazard modeling in both cohorts using established prognostic factors such as sex and histologic subtype (BWH: HR=2.9, p=0.003; TCGA: HR=3, p=0.003; BWH+TCGA: HR=2.3, p=0.002). Pathway analysis between high WCA burden vs. low WCA burden revealed down-regulation of genes associated with immune cell signaling and infiltration as well as up-regulation of genes related to cell-cycle and DNA repair.

Conclusion: MPM tumors display a wide distribution of chromosomal CNAs. A WCA score was developed to determine potential associations between CNAs and clinical characteristics of the patients. We found that patients with tumors having high WCA burden had a shorter survival than patients with tumors showing low WCA burden. Therefore, the number of chromosomal CNAs may be a tool to stratify patient prognosis.

P109: Implication of CCL5-CCR5 Axis in Malignant Pleural Mesothelioma Chemoresistance

Gerardelli L

1The Laboratory Of Tumor And Development Biology, University Of Liège, Liège, Belgium

Poster Session, Virtual, May 7, 2021

Implication of CCL5-CCR5 axis in Malignant Pleural Mesothelioma Chemoresistance.

GERARDELLI L. (1), BELLEFROID M. (1), SEPUIT C. (1), VANWINGE C. (2), NOEL A. (1) and CATALDO D. (1, 3)

(1) Laboratory of Tumor and Development Biology, University of Liège, Belgium
(2) Giga-cell imaging, University of Liège, Belgium
(3) Department of Respiratory diseases, CHU Liege and University of Liege, Belgium

Background: Malignant pleural mesothelioma (MPM) is an aggressive cancer with limited treatment options. Despite advances in immunotherapy, the standard treatment consists of chemotherapy combining pemetrexed and cisplatin. Unfortunately, in a majority of cases, tumor chemoresistance limits average patients’ survival to one year.

C-C Motif Chemokine Ligand (CCL5) is a chemokine overexpressed in various types of cancer (breast, colon). CCL5 interaction with its main receptor, C-C Motif Chemokine Receptor (CCR5), increases tumor development.

CCR5 is overexpressed in various cancers (breast, cervix,..) and pharmacological inhibitors are currently studied in clinical trials in triple negative breast cancer and colon cancer.

Evidence for a potential role of CCL5 in tumor resistance to chemotherapy is still scarce. Nevertheless, in ovarian, head and neck, and prostate cancer, cisplatin treatment was shown to induce the production of CCL5 by stromal cells. In head and neck cancers, the secretion of CCL5 by tumor tissue recruited tumor-associated macrophages (TAMs) expressing CCR5 and producing growth factors.

Therefore, CCL5-CCR5 axis might be linked to cisplatin resistance in mesothelioma.

Methods: To determine if CCL5 and CCR5 are associated in mesothelioma cisplatin resistance, we generated cisplatin-resistant human and mouse mesothelioma cells. These cells were assessed in vitro and in vivo to better understand mechanisms leading to cisplatin resistance in mesothelioma.

Results: In vitro, measurement of CCL5 expression in conditioned media of murine mesothelioma cells (AB12, PM27) and human cells (H28, MSTO-211H) showed that cisplatin-resistant cells secreted higher amounts of CCL5 as compared to parental cells. Furthermore, none of these cells expressed CCR5, CCR1 and CCR3. Stimulation with increasing doses of recombinant CCL5 did not influence cell viability.

BALB/C mice were subcutaneously injected in both flanks with cisplatin-resistant and parental AB12 cells. Cisplatin-resistant tumors showed increased growth rate and higher CCL5 and CCR5 expression as compared to their parental counterparts.

Flow cytometry analysis of tumors generated after subcutaneous injection of parental and resistant showed
an increased recruitment of F4/80 macrophages of M2 phenotype (CD206 positive cells) when resistant cells were injected as compared to parental cells. M2 macrophages from subcutaneous tumors express CCR5 and higher levels of this receptor were measured in tumors generated after resistant cell subcutaneous injection.

Conclusion: In conclusion, our results suggest that the CCL5-CCR5 axis might contribute to mechanisms leading to cisplatin resistance in MPM. These results also underline the potential involvement of changes in tumor microenvironment in resistance to chemotherapy. Our preliminary data identified M2 macrophages that express CCR5 as potentially involved in these mechanisms. Our future researches will focus on the roles played by M2 macrophages and molecular pathways leading to cisplatin resistance in MPM.

P110: Antidepressants Targeting the Ubiquitin-proteasome-autophagy Pathway

Patergnani S1, Nicoli F2, Maniscalco P3, Tamburini N3, Torreggiani E1, Tanji M4, Wieckowski M5, Alberto Scirè C6, Gavioli R2, Cavalleisco G3, Pass H7, Tognon M1, Yang H4, Carbone M4, Giorgi C1, Pinton P1

1Department of Morphology Surgery and Experimental Medicine, Section of Pathology Oncology and Experimental Biology, Laboratory for Technologies of Advanced Therapies (LTTA), University of Ferrara, Ferrara, Italy, 2Department of Life Sciences and Biotechnology, University of Ferrara, Ferrara, Italy, 3Department of Morphology, Experimental Medicine and Surgery, Section of General and Thoracic Surgery, Sant’Anna Hospital, University of Ferrara, Ferrara, Italy, 4Thoracic Oncology Program, University of Hawaii Cancer Center, Honolulu, United States, 5Department of Biochemistry, Nencki Institute of Experimental Biology, Warsaw, Poland, 6Section of Rheumatology, Department of Medical Sciences, University of Ferrara, Ferrara, Italy, 7New York University, Langone Medical Center, New York, United States

Poster Session, Virtual, May 7, 2021

Objectives: We investigated the anti-autophagic effects of ADs (desmethylclomipramine [DCMI], sertraline, clozapine and haloperidol) in primary MM cells derived from patient’s biopsies to test whether these drugs would increase the activity of chemotherapy in MM by Ca2+ dependent induced apoptosis.

Methods: We established primary human MM cell cultures from MM patients biopsies; moreover we established cell cultures of primary benign human mesothelial cells (HM, control) from pleural fluids of individuals with non-malignant conditions. We used primary cells, rather than cell lines, to limit the possibility that the results might be influenced by mutations occurring during extensive passage of cells in tissue culture. Cell lines were used to validate the results.

Results:
1) MM cells display increased activation of autophagy compared to HM cells;
2) We found that in MM cells, autophagy induces the degradation of type III inositol 1,4,5-trisphosphate receptor (IP3R3), the calcium (Ca2+) channel that modulates Ca2+ release from the endoplasmic reticulum (ER) to the cytosol and mitochondria, reducing apoptosis;
3) Pemetrexed and cis-Platinum cause the release of Ca2+ from the ER to mitochondria that causes tumor cell death – i.e., we discovered a novel mechanism of activity of these drugs;
4) Several antipsychotic/antidepressant drugs (ADs), DCMI, sertraline, clozapine and haloperidol, inhibit autophagy and thus increase apoptosis in MM cells treated with Pemetrexed and cis-Platinum, by increasing IP3R3 – i.e., we discovered new mechanism of ADs activity;
5) An initial analysis on a cohort of MM patients suggested an improved survival of mesothelioma patients treated with pemetrexed-cis-platinum who were also receiving ADs therapy.

Conclusion: We discovered novel mechanisms of drug activities and we used this knowledge to sensitize mesothelioma to pemetrexed-cis-Platinum induced apoptosis.

We discovered that the chemo-resistance of MM cells is largely related to reduced levels or reduced activity of the IP3R3 receptor and consequent reduced Ca2+ mitochondrial concentrations that render MM cells unable to execute apoptosis under chemo treatments.
Our results suggest that ADs should improve response to chemotherapy in MM patients by sensitizing MM cells to Pemetrexed and cis-Platinum-induced apoptosis.

**Keywords:** antipsychotic/antidepressant drugs (ADs), calcium (Ca2+), autophagy, type III inositol 1,4,5-trisphosphate receptor (IP3R3), mitochondria

---

**P111: Selective Mesothelioma-Killing Ability of Novel Porphyrin-Based Photosensitisers in Photodynamic Therapy**

Bonsall S¹, Haywood-Small S¹, Turega S¹, Duly G¹, Porter J¹, Haywood-Small S¹

¹Sheffield Hallam University, Sheffield, United Kingdom

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Intra-operative pleural photodynamic therapy (PDT) has recently emerged as a promising option to improve the multimodal treatment outcomes for mesothelioma. PDT involves the prior administration of a photosensitising agent, which accumulates in the tumour. Local light illumination of the tumour activates the photosensitiser, in turn forming radicals and reactive oxygen products which ultimately triggers cell death. The search for new, improved photosensitisers is ongoing, especially as photosensitisers have now entered clinical trials for mesothelioma.

Therefore, the focus of this approach is to develop and validate novel photosensitisers, to selectively kill mesothelioma cells. This study is assessing the PDT effect of a panel of novel porphyrin derivatives in a panel of human mesothelioma cell lines.

**Methods:** MSTO-211H and NCI-H28 mesothelioma cell lines were evaluated alongside the non-cancerous human mesothelial cell line, Met-5a. Cell viability was initially determined using the WST-8 cytotoxicity assay and flow cytometry of Annexin V-FITC/PI stained cells confirmed the induction cell death.

**Results:** Data suggests that porphyrin C6 demonstrated most potency on the NCI-H28 cell line, while porphyrin C7 displayed the greatest potency on the MSTO-211H cell line. Both apoptotic and necrotic cell death was observed, this varied with incubation time, photosensitiser and cell line. The unexpected, poor photodynamic activity of photosensitisers with longer alkyl chains (C8) may have been due to aggregation; subsequently preventing cellular uptake.

**Conclusion:** Current investigations involve subcellular localisation of the photosensitisers and include validation in a 3D cell culture model system. Future directions will build on the developments, aiming to refine and validate a series of clinically viable, novel photosensitisers for mesothelioma PDT.

**Keywords:** Photodynamic Therapy, Novel Photosensitisers, Cell Death
**P113: Exploring microRNA and Exosome Involvement in Drug Resistant Malignant Pleural Mesothelioma**

**Johnson B¹, Zhuang L¹, Yuen M¹, Cheng Y¹**  
¹Asbestos Diseases Research Institute, Concord, Australia

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant Pleural mesothelioma (MPM) is a deadly thoracic malignancy and existing treatment options are limited. Chemotherapy, consisting of a combination of cisplatin and pemetrexed, remains the most widely used first-line treatment regimen for patients with unresectable MPM, but its clinical efficacy is hampered by drug resistance issues. We have previously shown that MPM cell lines transfected with microRNA-16 (miR-16) induces an enhanced sensitivity to chemotherapy drug treatment, however further investigation into cellular targets to further enhance MPM sensitivity to chemotherapy is warranted. Aberrant microRNA (miRNA) expression, survivin over-expression and exosome up-regulation are well known factors associated with drug resistance in many cancers, but their role in MPM drug resistance is largely unexplored. Therefore, this project aims to explore the involvement of miRNA, survivin and exosomes in drug resistant MPM cell lines.

**Methods:** The Asbestos Diseases Research Institute (ADRI) houses an extensive mesothelioma biobank, consisting of over 40 primary mesothelioma cell lines, which was utilised as the primary source of MPM cells for the drug response assays carried out in this study. All MPM cell lines were transfected with miR-16 prior to drug treatment. To assess a broad spectrum of drug response in mesothelioma, we treated the MPM cell lines with a range of chemotherapeutic drugs, including cisplatin, gemcitabine, vinorelbine; as well as the survivin small molecule inhibitor (YM155), and the exosome inhibitor (GW4896). Following drug treatments, MPM drug resistance in response to chemotherapy drug treatment, and survivin and exosome inhibition, was determined via the alamarBlue cell proliferation assay. Dose response curves were generated with GraphPad Prism and IC50’s were subsequently interpolated. Background studies of survivin and exosome expression were taken into consideration for the assessment of chemotherapy drug response in the MPM cell lines.

**Results:** Our previous study indicated that the restoration of miR-16 could induce sensitivity to chemotherapeutic drugs in MPM cell lines that are resistant to cisplatin, gemcitabine and vinorelbine. In agreement with our previous investigation, this current study similarly demonstrated an enhanced drug sensitivity for MPM cell lines for most of the tested chemotherapeutic drugs. Additionally, we found that miR-16 sensitisation was further enhanced in MPM cells treated with the small molecule inhibitor (YM155), which was determined to be un-related to the basal survivin expression of the cells. All MPM cell lines appeared to have up-regulated exosome secretion, however MPM cells treated with the exosome inhibitor exhibited no significant sensitisation to the chemotherapeutic drugs.

**Conclusion:** Restoration of miR-16 expression, in combination with the small molecule inhibitor (YM155), enhanced the sensitivity of the MPM cell lines to the chemotherapeutic agents. This suggests that both a loss in miR-16 and expression of survivin play a role in MPM drug resistance. Exosome involvement was not found to be associated with MPM drug resistance.

**Keywords:** chemotherapy drug, drug resistance, exosome, malignant pleural mesothelioma, microRNA, survivin
**Objectives:** The prognosis of malignant mesothelioma (MM) barely changed in the past 4 decades. The extremely hypoxic and heterogeneous tumour microenvironment of MM provides a perfect niche for cancer stem cells (CSCs) that promotes therapeutic resistance. The asbestos and hypoxia-induced chronic inflammation activate a crucial transcription factor, NFkB, which plays a pivotal role in maintaining CSCs, chemo-radio-resistance, and invasiveness. NFkB also triggers PD-L1 expression, allowing MM cells to evade the host immune system. Therefore, development of a drug simultaneously targeting hypoxia-NFkB-CSCs axis is of clinical significance.

Anticancer drug development is a laborious and expensive procedure (£1.2 billion/15 years), with high attrition rates due to toxicity issues, leading to high costs of anticancer drugs. Therefore, drug repurposing has become an attractive strategy for drug development in recent years.

We have shown that Disulfiram (DS), a clinically used anti-alcoholism drug, combined with copper (Cu) specifically eradicates CSCs and reverses chemoresistance. DS strongly chelates Cu to form a Cu-DDC complex, which is a potent inhibitor of NFkB and induces apoptosis by increasing reactive oxygen species (ROS). However, the clinical application of DS for cancer is hindered by its short half-life (4 minutes) in the bloodstream. Considering the infiltrating growth feature of MM, we developed an intraperitoneally injectable poly (lactic-co-glycolic acid) microparticle-encapsulated Disulfiram (PLGA-DS) for local treatment of MM.

**Methods:** Hypoxic cultures, Cytotoxicity assay, Flow cytometry, CSC markers, Western blot, sphere reformation, invasion/migration, LCMS, in vivo models of MM.

**Results:** MM cells cultured in hypoxia showed significant resistance to Pemetrexed and Cisplatin. Hypoxia increased the expression of CSC markers, NFkB, PDL-1 and enhanced the migration/invasion ability of MM. We verified the feasibility of scale-up in an industrial setting and produced GMP certified PLGA-DS at a size range of 800-900nm with 17.75% drug loading. We also confirmed the slow release of DS up to 6 days without particle aggregation.

PLGA-DS/Cu induced apoptosis in MM cell lines at low nanomolar levels (IC50s: 500-700nM) and synergistically reversed the hypoxia-induced resistance to cisplatin/pemetrexed. PLGA-DS/Cu eradicated CSC population and hypoxia-induced stemness, demonstrated by sphere reformation and CSC markers. PLGA-DS/Cu inhibited the hypoxia-induced NFkB and PD-L1 expression and blocked the migration/invasion ability of MM cells.

After injection of 5mg/kg PLGA-DS (i.p) and oral administration of 2mg/kg Copper gluconate, (3 times/week for three weeks), we observed a significant reduction in the tumour burden and the number of tumour nodules in MM xenograft mouse models. We detected a high concentration of both DS (6 mM) and Cu-DDC complex (5 mM) in the peritoneal wash and the bloodstream, indicating that that DS released from the PLGA particles can combine with Cu and exert its anticancer efficacy without degradation. All animals tolerated the PLGA-DS and Cu very well for at least 4 weeks without any adverse effects or toxicity to vital organs.

**Conclusion:** DS is an FDA approved drug and a perfect candidate for local treatment of MM. Our approach of encapsulated DS combined with the route of orphan indication, will speed up the approval process and enable quick translation DS for MM treatment.

**Pre-clinical development, Chemoresistance, Cancer stem cells, Hypoxia, Disulfiram, Drug Repurposing**

**P115: Malignant Mesothelioma with Loss of NF2: Are YAP and TAZ Rational Targets?**

Kulkarni A1,2, Vissers J1,2,3, Harvey K1,2,4

1The Peter MacCallum Cancer Centre, Parkville, Australia, 2The Sir Peter MacCallum Department of Oncology, the University of Melbourne, Parkville, Australia, 3University of Melbourne Centre for Cancer Research, Parkville, Australia, 4The Monash Biomedicine Discovery Institute, Monash University, Clayton, Australia

**Poster Session, Virtual, May 7, 2021**

**Objectives:** The role of NF2 as a key tumour suppressor in mesothelioma is well established, with approximately 50% of mesotheliomas exhibiting a loss of function mutation in the NF2 gene. NF2 has multiple functions, one of which is as an upstream regulator of the Hippo
signalling pathway, which represses tissue growth by antagonising the transcriptional coactivators and oncoproteins YAP and TAZ. Loss of NF2 function results in YAP and TAZ hyperactivation, which might promote mesothelioma development. Thus, YAP and TAZ are potential therapeutic targets for the treatment of NF2 deficient mesotheliomas.

In this study, our objective was to assess the potential for therapeutically targeting YAP/TAZ in mesothelioma. We aimed to evaluate the sensitivity of YAP/TAZ inhibition in reducing the proliferation and survival of mesothelioma cells with and without genetic aberrations in NF2.

**Methods:** Activity of YAP/TAZ was inhibited in mesothelioma cells through siRNA knockdown or treatment with chemical inhibitors. A panel of eight mesothelioma cell lines and non-malignant control cells were used in the study. In addition, an NF2 mutant isogenic system was generated using CRISPR/Cas9 mutagenesis. Levels of YAP and TAZ activity were measured through immunoblotting, immunofluorescence and RNA sequencing.

**Results:** Depletion of YAP and TAZ significantly impaired the viability of multiple mesothelioma cell lines. The three most sensitive cells to YAP/TAZ knockdown harboured mutations in NF2 and/or the Hippo pathway kinases LATS1/2. Interestingly, some cell lines with no known genetic aberrations in the Hippo pathway also displayed similar sensitivity to YAP/TAZ knockdown. Additionally, non-malignant Met5A cells showed a comparable level of sensitivity to YAP and TAZ knockdown as tumour-derived mesothelioma cell lines. All cell lines showed similar responses to treatment with the putative Hippo pathway modulators Simvastatin and Verteporfin, with the exception of MSTO 211H cells, which exhibited heightened sensitivity to Simvastatin.

In an NF2 mutant isogenic system, we observed decreased levels of YAP inhibitory phosphorylation, increased cytoplasmic-to-nuclear ratio of YAP localisation and enrichment for the YAP target gene signature in NF2 deficient cells. However, NF2 loss alone did not result in dependency on YAP for cell survival.

**Conclusion:** Our findings implicate that loss of NF2 drives YAP/TAZ hyperactivation in mesothelial cells, but this is not the key factor that determines dependency of such cells on YAP for survival, at least in our experimental settings. However, we find that some mesothelioma cells are more sensitive to YAP/TAZ inhibition than non-malignant cells, irrespective of their Hippo pathway mutation status. Accordingly, targeting YAP/TAZ may be a viable option for the treatment of mesothelioma, but predicting which patients will respond to YAP/TAZ inhibition is likely to require biomarkers other than NF2 mutation status.

**Keywords:** NF2, YAP, TAZ, Hippo pathway, Targeted therapy

---

**P116: Long-Fibre Carbon Nanotubes Induce a Higher Incidence of Malignant Pleural Mesothelioma in the MexTAg Transgenic Mouse Model, Replicating Asbestos-induced Mesothelioma**

Zacarias-Cabeza J¹, Chernova T¹, Craxton A¹, Sun X¹, Donaldson K², Greaves P³, Lake R³, Poland C³, Fisher S⁴, Willis A¹, MacFarlane M¹

¹MRC Toxicology Unit, University of Cambridge, Leicester, United Kingdom, ²MRC/University of Edinburgh (QMRI), Edinburgh, UK, ³Dept. of Cancer Studies, University of Leicester, Leicester, UK, ⁴The University of Western Australia/NCARD, Perth, Australia

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Animal models are important tools for exploring cancer biology and identifying/testing novel therapeutic strategies. In humans, Malignant Pleural Mesothelioma (MPM) is associated with exposure to Asbestos fibres, whereby long Asbestos fibres fail to clear through the lymph system and are retained in the pleurae of exposed individuals leading to the development of MPM with a latency period of up to 40 years. The MexTAg transgenic mouse model of mesothelioma replicates many aspects of human mesothelioma, including induction by Asbestos (Robinson et al, Eur. J. Cancer 2011). Furthermore, mesotheliomas observed in MexTAg mice are comparable at the molecular level with those in wild-type mice. Manufactured long-fibre carbon nanotubes (CNTs) are similar to Asbestos in terms of their high aspect-ratio, and thus may pose an Asbestos-like inhalation hazard (Chernova et al, Curr. Biol. 2017). Using
the MexTAg transgenic mouse model, we have explored the potential for occupationally-relevant doses of CNTs to induce the development of pleural mesothelioma and compared the molecular changes that occur over time at the mesothelium to those induced by Asbestos.

Methods: Using MexTAg transgenic (mouse line 304i; Robinson et al, Eur. J. Cancer 2011) and wild-type (WT; C57/Bl6) mice, together with a model of direct injection into the pleural cavity (the main site of mesothelioma development), we have compared the overall survival time, the incidence of mesothelioma and the molecular changes that occur at the mesothelium after exposure to long-fibre CNT or Asbestos over 20 months following intra-pleural injection.

Results: We show that CNT-induced respiratory symptoms, encompassing chronic inflammation and/or fibrotic lesions, are accelerated in MexTAg transgenic mice compared to WT mice. In line with this, and consistent with what that demonstrated previously for Asbestos, the incidence of CNT-induced MPM was significantly increased in MexTAg mice. Significantly, when administered at an equivalent mass dose, CNTs induced a higher incidence of malignant mesotheliomas compared to Asbestos. Histopathological analysis showed that Mesotheliomas in the MexTAg mice were more commonly sarcomatoid subtype rather than epithelioid. Importantly, cell lines derived from CNT- or Asbestos-induced MexTAg mouse pleural effusions displayed characteristic molecular hallmarks of human mesothelioma. Moreover, on re-injection into the peritoneum of MexTAg mice, these mesothelioma cell lines again induced tumours which on histological analysis retained key histological/molecular features of the original tumour. These CNT- or Asbestos-induced mesothelioma cell lines therefore provide a unique resource for further detailed molecular profiling and the identification of potential targets for therapeutic intervention.

Conclusion: The MexTAg transgenic mouse provides a valuable model to study Asbestos or CNT-induced malignant mesothelioma, as this model develops disease in a short time-frame compared to WT mice. Importantly, using direct pleural injection of occupationally-relevant doses, we now show for the first time that long-fibre CNTs induce mesothelioma in MexTAg mice with an increased incidence compared to Asbestos. Using this model, we have established both CNT- and Asbestos-induced pleural mesothelioma cell lines which on re-injection in vivo replicate the original tumour, thus providing a valuable tool for in vivo testing of potential therapeutic interventions.

Keywords: In Vivo Model, MexTAg Mouse, Pleural Mesothelioma, Carbon Nanotubes, Asbestos

P117: Homozygous Deletion of CDKN2A in Malignant Mesothelioma: Diagnostic Utility, Patient Characteristics and Survival in a UK Mesothelioma Centre

Marshall K1, Jackson S1, Jones J1, Holme J1, Lyons J1, Barrett E2, Taylor P3, Bishop P4, Hodgson C5, Green M5, Telford N5, Evison M1

1Pleural Medicine, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, United Kingdom, 2Department of Medical Statistics, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, United Kingdom, 3Department of Medical Oncology, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, United Kingdom, 4Department of Cellular Pathology, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, United Kingdom, 5Department of Cytogenetics, The Christie NHS Foundation Trust, Manchester, United Kingdom

Poster Session, Virtual, May 7, 2021

Background: Detection of homozygous deletion of the p16 gene (CDKN2A) by fluorescence in situ hybridization (FISH) has been investigated as an ancillary technique in the diagnosis of malignant mesothelioma.

Method: This retrospective study reviewed the results of all p16 FISH tests performed at a regional mesothelioma centre from February 2012 to November 2019 in cases of possible mesothelioma to examine the diagnostic utility of this test as well as patients characteristics and survival in p16 FISH positive mesothelioma versus p16 FISH negative mesothelioma.

Results: P16 FISH testing was requested in 216 pathological samples in the study period. The test failure rate was 4% (10/216). Median time from request to result
was 10 days (IQR 7-13, range 1-30). The sensitivity, specificity, NPV and PPV were 60%, 100%, 39% and 100% respectively. There were no false positive results and this genetic aberration was only detected in cases of mesothelioma. The prevalence of p16 FISH positive mesothelioma was higher in cytological specimens compared to histological specimens (75% vs 58%, p=0.03) and lower in women compared to men (33% vs 66%, p=0.003). P16 FISH positive mesothelioma was associated with significantly worse survival (median overall survival 285 vs 339 days, p=0.0018). This remained significant after adjusting for confounding variables (OR 4.4, 95%CI 1.84-11.14, p=0.001).

Conclusions: In this study, 60% of mesotheliomas harbour a homozygous deletion of CDKN2A and can be accurately, reliably and efficiently identified by p16 FISH testing. This test can be embedded within routine practice in mesothelioma pathways to enhance diagnostic accuracy.

**P118: Novel Over-expressed Genes in Malignant Pleural Mesothelioma Cells as Selected Targets for Innovative Therapies**

Morani F1, Bisceglia L1, Dell’Anno I1, Barbuti C1, Melaiu O1, Silvestri R1, Landi S1, Gemignani F1

1University Of Pisa, Department of Biology, Pisa, Italy

Poster Session, Virtual, May 7, 2021

**OBJECTIVES.** Malignant pleural mesothelioma (MPM) is a rare aggressive chemotherapy-resistant tumor with a bad prognosis and still without effective therapies. The short-term goal of the present research project is to detect novel genes playing a role for the maintenance of the malignant phenotype, highlighting novel molecular targets for future therapies (long-term goal). In order to identify the MPM-driver genes we used the strategy of identifying those with an aberrant over-expression in MPM specimens, as compared to normal pleura. Thus, we performed an integrated gene expression analysis on RNAseq data of MPM patients from TCGA dataset and reference samples from GEO. Gene lists were further refined by published transcriptome studies on MPM, a functional enrichment analysis and the correlation between expression and patients’ overall survival (OS). A final list of 15 genes was detected. Among them, we selected a short list of genes to be further investigated along with other 4 genes previously selected from literature on the basis of their already known deregulation in other tumors.

**METHODS.** In this project, we screened the protein expression of the 15 over-expressed genes and the 4 selected genes from literature by Western Blotting assay in several mesothelioma cell lines: Mero-14, Mero-41, Mero-95, ZL-55, REN, MSTO and an immortalized cell line of the mesothelium (Met5A) as non-malignant mesothelial model. A way to evaluate the driver role in carcinogenesis for a given gene is to cause a functional knock-down using small interfering RNA (siRNA). If the gene is important in driving the malignant phenotype, measurable effects should be observed after 48-72h from silencing, such as either a reduced proliferation, a reduced invasive capacity, or increased apoptotic rates.

The migration capacities and the proliferation were measured with the IncuCyte® cell migration assay and proliferation assay, respectively. Moreover, to evaluate the apoptosis we used IncuCyte® Caspase-3/7 Apoptosis reagent or Annexin V reagent. The amount of fluorescence produced was proportional to the number of dead cells.

**RESULTS.** We confirmed the protein over-expression of 7 of 15 selected genes at least in 3 mesothelioma cell lines. Among them, we selected SPARC, UHRF1, BAG2 and MDK for gene silencing. Moreover, we confirmed protein over-expression of the 4 genes selected from literature (LAMC1, ACSL1, PGM1 and IL-18) carrying out also their gene silencing. Functional effects of gene silencing were monitored by IncuCyte® cell migration/proliferation / apoptosis assays. Preliminary results showed a limited effect of single gene silencing of the selected targets. More analyses are ongoing also by combining groups of siRNAs for studying the interactive effects.

**CONCLUSION.** A better understanding of the molecular mechanisms involved in MPM carcinogenesis is urgently needed to design successful therapies that could offer MPM patients a real clinical benefit. To this purpose, the over-expressed genes might be the most interesting targets for drug design.

**Keywords:** MPM, driver-genes, gene silencing, over-expressed genes, Incucyte assays
P119: Metabolic Profiling of Primary Mesothelioma Cell Lines to Elucidate a Network of Tumorigenic Processes

Olanipekun M1, MacFarlane M2, Willis A3, Cookson W1, Moffatt M1, Dumas M1

1Imperial College London, London, United Kingdom, 2MRC Toxicology Unit, Cambridge University, Leicester, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: Malignant mesothelioma (MM) is a devastating disease linked to asbestos exposure. Genomic markers of MM have been well explored and attempts have been made to target these aberrations. However, there is still a lack of exploitable, mechanistic markers of this disease. Metabolic profiling has implicated metabolites in various cancers, mediating many pathways. However, the metabolome of MM has yet to be characterised. Metabolic profiling of MM could reveal mechanisms of disease and metabolic vulnerabilities. As such, an in-house platform was developed to extract and profile metabolites from MM cell lines.

Methods: Two commercially-available cell lines (MSTO-211H and NCI H2052) were cultured on 6-well plates then were quenched and lysed with cold methanol (-80°C), then dried for analysis via gas chromatography-mass spectrometry (GC-MS). This semi-quantitative GC-MS analysis utilised the Fiehn compound library for spectral metabolite identification.

Results: Initial attempts to profile metabolites highlighted
variable growth rates among the cell lines. This method was improved by adjusting cell line seeding densities based on cell line doubling times to allow for comparisons. In addition, steps to quantitate the lysed cells were implemented into the extraction protocol. These quantitative methods compared involved either adherent or suspended cells. When suspended, cells could be counted and weighed as cell pellets prior to quenching. Cells were also quantified by total protein following lysis with methanol. The results suggested more metabolites could be extracted from adhered cell lines than suspended cells.

**Conclusion:** A total of 83 metabolites could be identified in cell extracts. Growth rate variation could be minimised by seeding cells at the maximal yield of the well (1x10^6 cells) with incubation for 24 h. This protocol successfully extracted and analysed metabolites from commercial cell lines and can be further developed to facilitate cell line comparisons and accurate cell quantification. This in-house profiling platform can be used to analyse MM cell lines via GC-MS and can be applied to primary MM cell lines, to evaluate a myriad of culture conditions and treatments.

**Keywords:** Malignant mesothelioma, metabolomics, cell lines, GCMS, metabolic profiling, semi-targeted

**P121: Targeting Thymidylate Synthase mRNA with a Novel Berberine Derivative in Malignant Mesothelioma**

**Plasencia C**, Lombardi P², Garcia V¹, Jimenez A³, Ciudad C³

¹Applied Research Using Omic Sciences, Barcelona, Spain, ²Naxospharma, srl, Milano, Italy, ³Department of Biochemistry and Physiology and IN2UB, University of Barcelona, Barcelona, Spain

**Poster Session, Virtual, May 7, 2021**

The overexpression of the Thymidylate Synthase (TS), an essential enzyme for DNA synthesis and repair, has been associated with resistance to pemetrexed-based chemotherapy in malignant mesothelioma (MM) patients. More recent evidences suggest the direct contribution of the enzyme in the epithelial to mesenchymal transition in pemetrexed-resistant cancer cells, suggesting TS overexpression behaves as an oncogene directly involved in bad prognosis.

**Objectives:** Suppression of TS nascent protein offers then, a possible therapeutic opportunity to correct/compenstate the aberrant expression in MM cancer cells, overcoming resistance phenotype and representing an alternative for refractory patients. We have developed and patented, a novel class of chemotherapy agents that specifically target TS-mRNA by binding it and suppressing TS protein expression.

**Methods:** To further elucidate the specific molecular recognition of TS-mRNA by these compounds, the interacting mRNA regions were narrowed to the start codon described for TS. A combination of site-directed RNA mutagenesis and target-binding assays are being used to prove the target specificity. We have also explored the effects of the compound on signaling pathways implicated in MM drug resistance. Thus, we explored EGFR, PI3K/AKT/mTOR and ERK signaling pathways as they are often deregulated in mesothelioma. Cell cycle arrest checkpoints, apoptosis and autophagy markers were also evaluated.

**Results and Conclusion:** Results so far, evidenced that we are in front a novel “first-in-class” compounds with great efficacy that represent a promising alternative to current TS inhibitors for the use as monotherapy and/or in combination with existing therapies to overcome TS-related resistance development.

**Keywords:** mesothelioma, mRNA, thymidylate synthase, signalling pathway

**P122: The Role of Mesothelioma-associated Fibroblasts in Tumor Growth**

**Ries A**, Flehberger D¹, Schelch K¹, Pirker C¹, Hoda M², Berger W¹, Grusch M¹

¹Institute of Cancer Research, Department of Medicine I, Medical University of Vienna, Vienna, Austria. ²Division of Thoracic Surgery, Department of Surgery, Medical University of Vienna, Vienna, Austria

**Poster Session, Virtual, May 7, 2021**

Objectives: Unlike the majority of cancers, malignant pleural mesothelioma (MPM) mostly exhibits mutations in tumor suppressor genes, such as NF2 or BAP-1,
and rarely shows alterations in tumor-promoting protooncogenes. The highly malignant nature of MPM in the absence of driver oncogenes indicates a supply of extrinsic tumor-stimulating molecules by cancer-associated cells and suggests a substantial influence of the tumor microenvironment in MPM. Cancer-associated fibroblasts (CAFs), the most abundant cell type of the tumor stroma, have been shown to impact various cancers by promoting tumor cell growth, invasiveness or therapy resistance. However, respective data for MPM is still very limited, and the role of mesothelioma-associated fibroblasts (MAFs) in particular has not been studied so far. Here, we focus on the influence of MAFs on MPM aggressiveness and hypothesize that MAFs supply tumor cells with important extrinsic signaling molecules to promote malignant behavior.

**Methods:** We isolated primary MAFs from tumor specimens of MPM patients and verified them by morphology as well as on the DNA and RNA level. To this end, we examined their genomes for amplifications and deletions using array-based comparative genomic hybridization and investigated the expression of common CAF marker genes via expression microarrays and quantitative real-time PCR. Since CAFs have been shown to influence cells by modifying their surrounding extracellular matrix, we investigated MAF-induced effects on MPM cells in 2D co-cultures as well as in 3D co-culture models with both cell types being embedded in a collagen matrix. A retrovirus-mediated introduction of GFP into the genome of the tumor cells enabled tracking them in culture.

**Results:** The isolated MAFs exhibit a long, typical fibroblast-like cell shape and possess normal genomes without various amplifications and deletions typical for MPM cells. They express multiple CAF markers such as alpha-smooth muscle actin or fibroblast activation protein, and lack MPM marker expression, like mesothelin. The presence of MAFs significantly enhanced proliferation of tumor cells in 2D co-cultures as well as in 3D co-culture models with both cell types being embedded in a collagen matrix. A retrovirus-mediated introduction of GFP into the genome of the tumor cells enabled tracking them in culture.

**Conclusion:** We were able to isolate and characterize patient-derived primary MAFs, providing a good and exceptionally rare platform for further experiments. Our data shows great impact of MAFs on MPM cell growth and indicates a substantial role of MAF in driving MPM malignant behavior.

### P123: Developing a Novel Genetically Engineered Mouse Model of Malignant Pleural Mesothelioma

**Rooney C**1, Gyuraszova K1, Farahmand P1, Monteverde T2, Duffin R3, Blyth K1, Berns A4, MacFarlane M3, Murphy D1

1University Of Glasgow, Glasgow, United Kingdom, 2CRUK Manchester Institute, Manchester, United Kingdom, 3MRC Leicester, Leicester, United Kingdom, 4University of Edinburgh, Edinburgh, United Kingdom, 5Netherlands Cancer Institute, Amsterdam, Netherlands

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant Pleural Mesothelioma (MPM) is an aggressive and pro-inflammatory cancer. It is clinically difficult to diagnose and is characterised by a long latency period. Thus most studies are restricted to end-stage disease and little is known about the pre-malignant process. Current MPM mouse models to interrogate this are hampered by long latency (in asbestos only models) and variable penetrance/ off target effects in existing transgenic models.

Our aim was to develop a novel genetically engineered mouse model that combines deletion of the major tumour suppressors lost in human MPM with intra-pleural injection of asbestos. This model will allow us to investigate how mutagenesis combines with fibre-induced inflammation to drive disease evolution.

**Methods:** We used genetic engineering to develop an accelerated mesothelioma mouse model that combines intrapleural injection of asbestos with pleural-restricted, CRE-mediated deletion of the key tumour-suppressor genes (TP53, NF2, CDKN2A) that are lost in human MPM. Multi-modality imaging was performed (MR-PET and ultrasound) to non invasively track disease progression. Tissue was analysed by immunohistochemistry and flow cytometry.

**Results:** Intra-pleural injection of asbestos dramatically accelerates mesothelioma development in mice triple deleted for NF2, Cdkn2a and Tp53, with all mice succumbing to malignant disease within 3-4 months (Figure 1). These mice develop lesions in the mesothelial lining of the thoracic cavity accompanied with pleural effusions that recapitulates human MPM. IHC analysis
shows positive staining for mesothelioma markers, e.g. pancytokeratin, vimentin and WT-1. Positive macrophage staining (F4/80) strongly indicates involvement of inflammatory component.

**Conclusion:** This is the first physiologically intact and anatomically accurate model of MPM that combines asbestos-driven chronic inflammation with loco-temporal deletion of relevant genes and is 1) a unique platform to investigate early and late stage events in the inflammatory evolution of MPM and 2) a rational and rapid platform for testing therapeutic approaches prior to clinical trials.

**Keywords:** asbestos, genetically engineered mouse model, mesothelioma

---

**P124: Impact of MET Amplification and Expression on Treatment Outcome in Malignant Mesothelioma**

**Santoni-Rugiu E1,4, Ravn J2,4, Lü M3,4, Jakobsen J3,4, Sørensen J1,4**

1Dept. of Pathology, Rigshospitalet, Copenhagen Univ. Hospital, Copenhagen, Denmark, 2Dept. of Thoracic Surgery, Rigshospitalet, Copenhagen Univ. Hospital, Copenhagen, Denmark, 3Dept. of Oncology, Rigshospitalet, Copenhagen Univ. Hospital, Copenhagen, Denmark, 4Danish National Mesothelioma Center, Rigshospitalet/ Copenhagen Univ. Hospital, Copenhagen, Denmark

**Poster Session, Virtual, May 7, 2021**

Objectives: The hepatocyte growth factor tyrosine-kinase receptor MET is a potential therapeutic target in several cancers, in which it can be activated by various mechanisms, including gene copy number gain (GCNG)/amplification (GA) and/or protein overexpression that may respond to MET inhibitors. Our group at the Danish National Mesothelioma Center has recently shown by strict criteria for fluorescence in-situ hybridization (FISH) and immunohistochemistry (IHC), that MET is overexpressed in >30% of malignant mesotheliomas (MMS), partly because of MET GCNG/GA. In this study we examined whether MET aberrations had prognostic impact or predicted likelihood of response to chemotherapy by comparing two MM-patient groups with and without MET aberrations treated during 2015-2017, i.e. with 3-5 years follow-up.

**Methods:** MET expression status was assessed on formalin-fixed paraffin-embedded diagnostic tissue biopsies with > 50% of tumor cell content, obtained from a total of 60 consecutive, previously untreated patients with epithelioid (EMM) or biphasic (BMM) MM. Tissue samples from 30 patients displayed MET-overexpression by IHC (CONFIRM SP44 anti-MET mAb, Ventana; immunoscores of 2+/3+ in ≥ 50% cells) with/concomitant MET GCNG/GA detected by FISH (Zyto-Light SPEC MET/CEN7 dual-color probe; Zytovision), as previously reported (Jakobsen JN et al, Oncotarget 9(40):26195-208, 2018). These MET-positive cases were matched to 30 MET-negative MM patients concerning gender, age, performance status, histologic subtypes, stage, and treatment (chemotherapy alone or chemotherapy plus pleurectomy), and compared with respect to outcome such as response to chemotherapy, and overall survival (OS).

**Results:** As previously observed, MET-overexpression was detected in EMMs and epithelioid but not sarcomatoid component of BMMs. The 30 MET-positive patients were comparable to the 30 MET-negative with respect to gender (male 77% vs. 83%), median age (69 years each), Performance Status 0 (50% vs 47%), stage IV (7% vs 14%), epithelioid subtype (77% vs. 70%), and treatment (chemotherapy alone or chemotherapy plus pleurectomy in 53% vs 57%). With respect to response to chemotherapy (either neoadjuvant or for advanced disease), this was observed in 37% of
MET-positive vs. 70% MET-negative cases (p=0.04), while median OS was 20 months vs. 27 months (p=0.934), respectively. A multivariate regression analysis revealed independent impact upon survival for gender (p=0.002) and stage (p=0.041), and borderline significance for pleurectomy (p=0.057), but not for MET-status (p=0.877).

**Conclusion:** We confirmed that MET aberrations, such overexpression and GCNG/GA, predominantly occur in EMMs. In the two matched cohorts of MET-positive and MET-negative MMs, the former revealed lower response rate and a non-significant trend towards shorter OS. A multivariate regression analysis did not reveal independent significant impact of MET status upon OS. A trend towards negative impact on OS in MET-positive patients may be due to MET being driver of proliferation and to some extent causing insensitivity to chemotherapy. If validated in larger cohorts, the results suggest a possibility of treating MET-positive MM by tyrosine kinase inhibitors, as currently evaluated in other malignancies, e.g. in NSCLC

**Methods:** YB-1 knockdown was performed using YB-1 specific siRNA. YB-1 overexpression was achieved by a doxycycline-inducible, retroviral construct, which was stably introduced into MPM cell lines. Cell migration was assessed by live cell videomicroscopy followed by manual single cell tracking and analysis using ImageJ and DiPer software, respectively. Three-dimensional spraying as well as gap formation were analysed by spheroid-based invasion assays. Cell cycle was assessed by flow cytometry and apoptosis by PI/Annexin V staining. Cell viability was measured by a SYBR green-based growth assay.

**Results:** We previously reported that YB-1 is up-regulated in MPM cell lines compared to non-malignant controls. YB-1 knockdown decreases MPM cell migration and invasion, hence we evaluated the impact of YB-1 overexpression on these phenotypes. MPM cell lines which overexpress YB-1 in a doxycycline-inducible manner showed increased cell scattering, migration and invasive sprouting. Additionally, when tumour spheroids were co-cultured with endothelial cells, YB-1 overexpression led to a significantly more extensive formation of gaps in the endothelial layer. On the other hand, we found that YB-1 knockdown also decreases MPM cell growth by apoptosis and cell cycle arrest. Importantly, combination with cisplatin or irradiation showed additive to highly synergistic (CI values < 0.5) combination effects.

**Conclusion:** In this study we report an important role of YB-1 in the regulation of cell migration and invasion, which are key characteristics of MPM, using YB-1 knockdown and overexpression cell models. Furthermore, YB-1 knockdown inhibits MPM growth but also sensitises cells to cisplatin and irradiation. These findings contribute to a better understanding of the biology of MPM and highlight YB-1’s potential as a therapeutic target.

**P125: YB-1 Is A Key Player in Aggressive Behaviour and Therapy Resistance in Mesothelioma**

**Schelch K**

1Institute of Cancer Research, Department of Medicine I, Medical University Of Vienna, Vienna, Austria, 2The ANZAC Research Institute, Concord Repatriation General Hospital, Sydney, Australia

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant pleural mesothelioma (MPM) is characterised by aggressive growth and frequent resistance to chemotherapy, poor prognosis for patients and limited therapeutic options. To establish potential new therapy targets, a better understanding of the MPM biology underlying these malignant behaviours is crucial. One potential candidate is the multifunctional oncprotein YB-1, which is often overexpressed in various cancers and associated with aggressiveness, metastasis and poor outcome.
P126: Inactivation of p21-activated Kinase 2 (Pak2) Inhibits the Development of Nf2-Deficient Malignant Mesothelioma

Sementino E1, Kadariya Y1, Cheung M1, Menges C1, Tan Y1, Kukuyan A1, Shrestha U1, Karchugina S1, Cai K1, Peri S1, Duncan J1, Chernoff J1, Testa J1

1Fox Chase Cancer Center, Philadelphia, United States

Poster Session, Virtual, May 7, 2021

Malignant mesothelioma (MM) is characterized by frequent somatic inactivation of the NF2 tumor suppressor gene. The NF2 gene product, Merlin, is implicated in several tumor-related cell pathways, including p21-activated kinase (PAK) signaling. Merlin is both a phosphorylation target for PAK and a negative regulator of this oncogenic kinase. Merlin loss results in PAK activation, suggesting that PAK inhibition could have therapeutic efficacy in Merlin-deficient tumors.

Objectives: The goal of this investigation was to test whether PAK inhibitors hold promise for the treatment of NF2-mutant tumors, as assessed using a preclinical MPM model.

Methods: Nf2f/f;Cdkn2a/f mice were crossed to mice with wild type or conditional knockout of Pak2, a highly expressed group I Pak member. Adenovirus expressing Cre recombinase was injected into either the thoracic or peritoneal cavities of cohorts of these animals to delete floxed alleles in the mesothelial lining, and then the mice were monitored for tumor development. RNA-seq and kinome profiling with protein kinase-capture beads were performed on Nf2-/-;Cdkn2a-/-;Pak2-/- versus Nf2-/-;Cdkn2a-/-;Pak2+/+ MM cells derived from these mice to assess transcriptional and kinase changes, respectively, connected with Pak2 loss.

Results: Mice with loss of Pak2 in the mesothelial lining showed a markedly decreased incidence and delayed onset and progression of both pleural and peritoneal MMs, as documented by Kaplan-Meier survival curves and in vivo bioluminescent imaging. RNA-seq analysis revealed that Nf2-/-;Cdkn2a-/-;Pak2-/- MM tumor cells showed downregulated expression of certain stem cell marker genes, such as Sox8 and Sox11, as well as genes involved in several oncogenic signaling pathways (e.g., Wnt, Hedgehog, Akt), when compared to Nf2-/-;Cdkn2a-/-;Pak2+/+ MM cells. When placed on ultra-low attachment plates, MM cells that retained Pak2, but not those with loss of this kinase, formed spheroids and expressed stem cell markers such as Sox2, Nanog, and Gli1. Kinome profiling of Nf2-/-;Cdkn2a-/-;Pak2-/- pleural MM cells revealed changes in the expression of multiple kinases indicative of an epithelial to mesenchymal transition, including upregulation of PDGFA and PDGFB; moreover, phosphorylation of the downstream target, STAT3, was demonstrated in multiple Nf2-/-;Cdkn2a-/-;Pak2-/- pleural MM cell lines grown in vitro.

Conclusion: Collectively, these findings suggest that Nf2-/-;Cdkn2a-/-;Pak2-/- MM tumor cells adapt in vivo by reprogramming their kinome and gene expression signature to bypass the need for Pak activity via the activation of other compensatory oncogenic pathways. The identification of such secondary pathways offers opportunities for rational combination therapies to circumvent resistance to anti-PAK drugs.

P127: Development of A Living Biobank of Patient-Derived Malignant Pleural Mesothelioma Organoid Models

Shamseddin M1,2, Frances H1, Rassl D3, Rintoul R3,4, Garnett M1, Marciniak S2

1Wellcome Sanger Institute, Hinxton, UK, 2Cambridge Institute for medical research, Cambridge, UK, 3Royal Papworth Hospital, Cambridge, UK, 4Department of Oncology, University of Cambridge, Cambridge, UK

Poster Session, Virtual, May 7, 2021

Introduction: Malignant pleural mesothelioma is an incurable cancer caused by exposure to asbestos. Although asbestos use is banned in many countries, the incidence of MPM is expected to rise in the coming decades due to the industrialisation of developing nations. The median survival time for mesothelioma remains poor, between 1 to 2 years and surgery and doublet chemotherapy with pemetrexed and cisplatin provides only minimal benefits. There is therefore a pressing unmet need for new effective therapies in this disease setting. For
these to be developed, improved preclinical models are required that effectively recapitulate many aspects of this disease.

Tumour-derived cell lines tend to lose the genetic and phenotypic characteristics of the primary tumour during long-term culture while animal models are costly, time consuming and unsuitable for high-throughput drug screening. Patient-derived tumour organoids have emerged as important preclinical models for precision medicine allowing the long-term growth and expansion of tumour cells in 3D culture. These models can recapitulate genomic alterations and histopathological features of the tumour of origin. Importantly, they are amenable to a number of experimental techniques including chemical and genetic perturbation screens. Large scale efforts, such as Human Cancer Models Initiative, are now attempting to derive and characterise panels of cancer organoids that recapitulate the diversity of patient population to better identify new therapeutic strategies for a variety of cancer types. To date, no method for mesothelioma organoid generation has been developed.

Objectives: We aim to develop a robust protocol for the derivation and propagation of malignant pleural mesothelioma organoids. We will use these to evaluate if such a model will recapitulate the genomic and phenotypic features of the original tumours and ultimately, use these models to identify novel therapies/drug targets for this disease.

Methods: In collaboration with MesobankK, we regularly receive fresh tumour tissue and pleural fluid from MPM patients. Following primary sample processing we attempt to derive and propagate the organoids in a 3-D matrix. To find the best medium condition for organoid derivation, we test different specialized media. In addition, we try to optimize the medium conditions using organoid formation and cell viability assays. From the developed organoids, samples are collected as fresh frozen or fixed at different time points for subsequent DNA sequencing and immunohistochemistry (IHC) staining.

Results: Three organoids lines have been generated and passaged 7 to >10 times within 3-6 months from 15 donors diagnosed with MPM. The results of our organoid formation assays show that different organoid models have different dependencies on growth factors and inhibitors. Most organoids show improved growth upon addition of EGF or FGF2. The organoids and their matched primary tumours have been sent for DNA sequencing and IHC.

Conclusion and future work: We have managed to develop 3 organoid lines from 15 donors diagnosed with MPM. Further work is on-going to verify that the organoid models retain the characteristics of original cancer tissue based on DNA sequencing and IHC staining results, which will be obtained in near future.

P128: Simultaneous Inhibition of Both BCL-XL and MCL-1 Provides a Potent Therapeutic Strategy for Treating Malignant Pleural Mesothelioma

Sun X1, Craxton A1, Bennett J2, Nakas A2, Cain K1, MacFarlane M1

1MRC Toxicology Unit, University Of Cambridge, Leicester, United Kingdom, 2University Hospitals of Leicester NHS Trust, Glenfield Hospital, Leicester, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: Malignant Pleural Mesothelioma (MPM) is an asbestos-related cancer; its clinical prognosis with standard of care therapy is poor, therefore, new approaches to target MPM are urgently required. Structure biology-based design of BH3-mimetics has produced compounds that can specifically inhibit individual members of the pro-survival BCL-2 family. Unfortunately, most mesothelioma cells express more than one member of the pro-survival BCL-2 family. Consequently, single-agent targeting is less effective. In this study, we investigate the therapeutic potential of combining two separate BH3-mimetics targeting different pro-survival BCL-2 family members to treat mesothelioma.

Methods: We have used 2D cell culture for conventional cell death assessment by flow cytometry, or a 3D MPM tumour explant model which crucially retains the tumour microenvironment. For the latter, freshly-resected mesothelioma tissue was cut into 2 mm3 cubes (tumour explants), allowing live tumours to be cultured ex-vivo with various therapeutic agents. Explants treated in this way for the indicated time periods were fixed and processed according to standard histology protocols and immunohistochemical labelling performed to assess cell
death using standard protocols. Images were acquired using a Hamamatsu slide scanner and image analyses carried out using VisioPharm software to quantify drug efficacy. CRISPR/Cas9 gene editing and analysis of bioenergetics using a Seahorse XF analyser (XFe96) were used to further dissect the mechanisms of cell death.

**Results:** Single-agent treatment with BCL2/BCL-XL (ABT-737) or MCL-1 (S63845) inhibitor alone failed to induce apoptosis in mesothelioma cells, both in 2D (conventional) and 3D (tumour explant) culture systems. However, combinatorial treatment with ABT-737 and S63845 induced significant apoptotic cell death, in a concentration-dependent manner. Single-agent treatment had little effect on either mitochondrial ETC-driven oxygen consumption (OCR) or glycolysis (ECAR). In contrast, the combination of ABT-737 and S63845 completely blocked uncoupler-stimulated OCR, which is dependent on mitochondrial outer membrane permeabilisation (MOMP) because co-deleting BAX/BAK reversed this effect.

**Conclusion:** These results recapitulate our previous findings, using either a metabolic switch (by inhibiting glycolysis with 2DG in combination with AKT inhibition) or siRNA targeting to downregulate MCL-1 and potentiate ABT-737-induced cell death in MPM cells which are normally resistant to ABT-737. Our studies also show that molecular interactions centred on BH3-binding play a key role in mitochondrial bioenergetics, as well as induction of cell death. Since BH3-mimetics are currently being evaluated in the clinic, our pre-clinical data in live MPM tumours demonstrates that simultaneous inhibition of BCL-XL and MCL-1 with BH3-mimetics achieves potent tumour killing in MPM.

**Keywords:** mesothelioma therapy, BCL-2, BH3 mimetics, apoptosis

**P130: Modulating the Local Tumour Microenvironment to Sensitise Mesothelioma to Chemotherapy**

**Tilsed C**1,2, Principe N1,2, Chin W1,4,5, Zemek R3, Fear V3, Forbes C3, Nowak A1,4,5, Fisher S1,2, Lake R1,2, Lesterhuis W1,2,3

1National Centre For Asbestos Related Diseases, UWA, Nedlands, Australia, 2School of Biomedical Sciences, UWA, Nedlands, Australia, 3Telethon Kids Institute, Nedlands, Australia, 4Medical School, UWA, Nedlands, Australia, 5Department of Medical Oncology, Sir Charles Gardiner Hospital, Nedlands, Australia

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Chemotherapy is the first line therapy for advanced mesothelioma, however treatment is predominantly palliative. Chemotherapy is also a key component of aggressive multimodality therapy. The mechanisms that drive an effective chemotherapeutic response are incompletely understood and there are no effective biomarkers that predict response in people with mesothelioma. Along with the direct cytotoxic effects of chemotherapy, the composition of the tumour microenvironment (TME) has been shown to influence treatment effectiveness. Immune cells and immunological mediators, in particular, can induce a TME that is either sensitive or resistant to chemotherapy. The ideal composition of the mesothelioma TME that is associated with an effective response to chemotherapy is unknown.

**Methods:** We developed a unique approach to determine the molecular characteristics of a responsive TME, by exploiting the fact that inbred mice bearing tumours derived from clonal cancer cell lines display dichotomous responses to treatment. We established that two bilateral AB1-HA murine mesothelioma tumours respond symmetrically, yet dichotomously to cyclophosphamide chemotherapy; both tumours either respond or they both do not. This allows for one tumour to be removed and analysed while its ‘fate’ is inferred from the response of the remaining tumour. Using this model, we performed RNA sequencing on tumours prior to chemotherapy to characterise the pre-treatment microenvironment of responding and non responding tumours. Computational analysis included differential expression, CIBERSORT and ESTIMATE RNAseq deconvolution algorithms, gene set enrichment analysis, pathway over-representation analysis and Ingenuity upstream regulator analysis. Identified pathways and regulators of response were therapeutically targeted in murine cancer models to modulate the response rate to chemotherapy.

**Results:** We found that responding tumours were enriched for inflammatory genes and significantly upregulated CD4+ T helper associated pathways. Using pathway analysis, we identified key upstream regulators that were predicted
to induce a cyclophosphamide sensitive TME which include cytokines and repurposable drugs. When CD4+ T cells were depleted or positive regulators of response were neutralized, the response to cyclophosphamide was completely abrogated. We hypothesise that targeting positive upstream regulators of response before treatment will sensitize a tumour to subsequent therapy by inducing a chemo-sensitive gene expression signature. In vivo experiments that pre-treat the TME with the aim of sensitizing the mesothelioma microenvironment to cyclophosphamide and other chemotherapies are currently ongoing.

Conclusion: These findings indicate that an inflammatory CD4+ T cell driven pre-treatment gene expression signature can serve as a predictive biomarker for response to cyclophosphamide chemotherapy in mesothelioma. Chemotherapy effectiveness in mesothelioma may be improved by pre-treating the TME to induce a gene expression signature associated with response.

Keywords: chemotherapy, RNA sequencing, biomarker, gene signature

P131: BAP1 Inactivation Alters Cellular Migratory Behaviour Suggesting the ARP2/3 Complex as a Therapeutic Target in MPM

Tripari M1, Barnett S1, Goate Z1, Kenyani J1, Silva L1, Querques F1, Herrmann A1, Kalirai H2, Sacco J2, Coulson J1

1Molecular Physiology & Cell Signalling, Institute of Systems, Molecular & Integrative Biology, University of Liverpool, Liverpool, UK, 2Molecular & Clinical Cancer Medicine, Institute of Systems, Molecular & Integrative Biology, University of Liverpool, Liverpool, UK

Poster Session, Virtual, May 7, 2021

Objectives: BAP1 is a deubiquitylase (DUB) and tumour suppressor with fundamental roles in gene transcription and protein stability. Somatic and germline BAP1 mutations are frequently observed in malignant pleural mesothelioma (MPM), resulting in catalytic inactivation of the protein and/or loss of nuclear localisation. BAP1 inactivation is found in ~60% of MPM cases and is most frequently associated with the epithelioid subtype. In the present study, we investigated BAP1-dependent alterations in cytoskeletal pathways identified by multi-omics analysis and phenotypically evaluated the role of BAP1-mutation in the migratory behaviour of MPM. This could provide a better understanding of local invasion, a characteristic clinical feature of MPM, and suggest new avenues for therapeutic intervention.

Methods: BAP1-dependent changes were profiled by SILAC mass spectrometry (MS) in isogenic BAP1w-/KO MeT5A mesothelial cells, which had been gene-edited to introduce a germline predisposition point mutation (w-) on one BAP1 allele and a promoter trap (KO) on the other. Immunoblotting analyses were performed to validate expression differences in isogenic MeT5A cells and to confirm clinical relevance across a large panel of patient-derived MPM cell lines sourced from MesobanK (www.mesobank.com) and the ATCC that were stratified by BAP1 status. Immunofluorescence was used to identify BAP1-dependent morphological changes. In addition, single-cell tracking and wound-healing assays were carried out to investigate the effect of BAP1 loss on individual and collective migration, respectively, and the response to specific inhibitors.

Results: Proteomic analysis revealed alterations in cytoskeletal pathways. Indeed, several components of the ARP2/3 complex, which is involved in the regulation of actin-based cell motility, were upregulated by sequential BAP1-mutation in isogenic MeT5A cells. Expression differences for components of this complex, ACTR2, ACTR3, ARPC2 and ARPC3 were validated by immunoblotting and, in agreement with these results, we observed that BAP1w-/KO MeT5A have more prominent lamellipodia. Moreover, functional assays of cell motility showed that BAP1w-/KO MeT5A are more migratory in vitro than their normal counterpart. Importantly, their migratory behaviour was significantly reduced by CK-666 (an ARP2/3 complex inhibitor) and Pimozide (an antipsychotic that may be repurposed for ARPC2 inhibition) and this is currently being confirmed by ARPC2 depletion. Furthermore, we showed that ARPC2 protein overexpression is recapitulated in BAP1-altered MPM cell lines, supporting the clinical relevance of these findings. Preliminary data for a pair of genetically similar BAP1-normal and BAP1-altered MPM cell lines further suggest that individual cell migration is affected in BAP1-altered
cells. We are currently investigating the mechanism by which ARPC2 is regulated upon BAP1 loss.

**Conclusions:** Using a novel isogenic mesothelial cell model, we found that ARPC2, along with other components of the ARP2/3 complex, is upregulated in a BAP1-dependent manner and this results in a more migratory phenotype. Collectively, our findings suggest a potential role for BAP1 in migration/invasion that could inform new therapeutic strategies in BAP1-mutated epithelioid MPM. Indeed, blocking ARPC2 function may reduce metastasis as well as local invasion. BAP1-dependent migratory behaviour will be further investigated in vivo using a recently established chick embryo model of MPM.

BAP1, migration, ARP2/3 complex

**P132: Defining and Targeting Tumor Associated Macrophages in Malignant Mesothelioma**

**Wu L,1 Kohno M,1 Murakami J1, Yun H1, Chan M1, Amjad S1, Aoki M1, Zhao Y1, Baciuc C1, Liu M1, Serre-Beinier V2, de Palma M3, Felley-Bosco E4, Yeung J1, Diaz-Mejia J5, Pugh T6, de Perrot M1,6**

1Toronto General Hospital, University Health Network, Toronto, Canada, 2Department of Thoracic Surgery, University Hospitals of Geneva, Geneva, Switzerland, 3EPFL, Swiss Federal Institute of Technology Lausanne, Lausanne, Switzerland, 4Laboratory of Molecular Oncology, University Hospital Zurich, Zurich, Switzerland, 5Princess Margaret Cancer Centre, University Health Network, Toronto, Canada, 6Department of Immunology, University of Toronto, Toronto, Canada

**Poster Session, Virtual, May 7, 2021**

Defining the ontogeny of tumor-associated macrophages (TAM) is an important step to develop selective targets. Two distinct macrophage populations are present in the mouse peritoneal and pleural cavity, the small monocyte-derived macrophage (SPM) and the large resident macrophage (LPM).

**Methods:** We investigated tumor-associated macrophages (TAM) in murine mesothelioma to identify SPM and LPM specific genes using microarray and single cell RNA sequencing (scRNA-Seq). Murine mesothelioma RN5 model, cell sorting, flow cytometry, fluorescent immunostaining, macrophage depletion by clodronate liposome or dicer1 conditional deletion were used. Programs including Transcriptome Analysis Console, Loupe cell, NetworkAnalyst, and Gsea/MSigDB were used for genomic analysis.

**Results:** We demonstrated that SPM rapidly accumulate in the tumor microenvironment (TME) after tumor cell challenge and contribute to the vast majority of M2 TAM. Selective depletion of M2 TAM by the conditional deletion of DICER1 in myeloid cells (D-/−) led to rejection of the tumor. On the other hand, sorted SPM M2 TAM led to rapid tumor development in vivo and in vitro with similar genetic property as the parental cells confirming their capacity to support tumor development. Transcriptomic and scRNA-seq analysis demonstrated that both SPM and LPM contributes to the TME by promoting the IL-2 STAT5 signaling pathway, inflammation and epitheliomesenchymal transition. SPM preferentially activated the KRAS and TNF-α NFκB signaling pathways, while LPM activated the IFN-γ response. The importance of LPM in the immune response was confirmed by depleting LPM with clodronate liposome in the pleural cavity and abrogating the memory immune protection. The SPM gene signature was readily identifiable in the pleural effusion and the tumor from patients with malignant pleural mesothelioma. Five genes, GPNMB, STAB1, TREM2, LAIR1, and MARCO could be potential therapeutic targets for immunotherapy.

**Conclusion:** These experiments demonstrate the importance of monocyte-derived TAM in mesothelioma and provide potential selective targets to implement in clinical trials.

Small/large peritoneal macrophages (SPM/LPM), Tumor-associated macrophages (TAM), Gene signature, Mesothelioma
**P133: Circulating Mesothelial Precursor Cells May Be a Novel Candidate for Screening and Prognosis in Malignant Pleural Mesothelioma**

**Wu L**, Duong B, Yun H, Zaeimi F, Felley-Bosco E, Kelley S, de Perrot M

1Latner Thoracic Surgery Laboratories, Division of Thoracic Surgery, University Health Network, Toronto, ON M5G 1L7, Canada, Toronto, Canada, 2Department of Chemistry, University of Toronto, Toronto, ON M5S 3H6, Canada, Toronto, Canada, 3Laboratory of Molecular Oncology, University Hospital Zurich, University of Zurich 8044 Zürich, Switzerland, Zurich, Switzerland, 4Institute for Biomedical and Biomaterials Engineering, University of Toronto, Toronto, ON M5S 3G9, Canada, Toronto, Canada, 5Department of Pharmaceutical Sciences, University of Toronto, Toronto, Ontario M5S 3M2, Canada, Toronto, Canada

**Methods:** Peripheral blood was collected from individuals who were exposed to asbestos and participated in our screening program with low dose CT scan (Asb, n=31), presented with a histological diagnosis of MPM (MPM, n=47) and healthy controls with no asbestos exposure (HD, n=10). Circulating MPCs were detected by immunomagnetic capture of Msln+CD34+CD90+. The device utilizes magnetic nanoparticles to capture and sort MPCs into 8 zones based on Msln expression. An expression index (EI) was calculated based on the zonal distribution of the captured cells and the number of MPCs extracted. The optimal EI cut-off value for diagnosis of MPM was determined by the area under the curve (AUC). Peripheral blood mononuclear cells were evaluated by flow cytometry and cytokines, chemokines and growth factors in the serum were evaluated by Luminex assay.

**Results:** Circulating MPCs in peripheral blood significantly increased in MPM patients compared to Asb and HD groups. The EI for circulating MPCs was 3678±1119 in MPM, 1057±209 in Asb, and 493±88 in HD (p<0.0001). EI in the patients with advanced stage MPM (4182±1644) was significantly higher than that in those with early stage disease (1830±390) (p<0.0001). EI was higher in patients with unresectable tumors (compared to surgical disease) (11526±2602 vs 6169±1217, p=0.0382), higher SUV (16912 ± 5849 vs 4946±660, p<0.0001) and nodal involvement (11296±2765 vs 22255 ±9361, p=0.0167). Circulating cytokines IFN-α2 and IFN-γ were down-regulated in MPM patients compared to Asb and HD groups, while the levels of Th2 cytokines (IL-1α/1Rα, IL-4, IL-5, IL-6, IL-9 andIL-13) were significantly higher in non-epithelioid mesothelioma than those with epithelioid subtype.

**Conclusion:** Circulating MPCs continuously increased after asbestos exposure and in mesothelioma compared to healthy control. Hence, MPCs could be a marker of mesothelial cell injury that culminate with the development and progression of mesothelioma. MPCs could be a novel candidate for screening and for prognosis in mesothelioma. Circulating Th2 cytokines could help to differentiate epithelioid from non-epithelioid MPM.

**Keywords:** Mesothelioma; Asbestos; Mesothelial precursor cells (MPCs); New target; Cytokines
**P134: E-cadherin Is Down Regulated in MM and the Expression of E-cadherin Leads to MM Cell Resistance to FAK Inhibitor**

Yuen M1, Zhuang L1, Sarun K1, Clarke C2, McCaughan B2, Lee K1,2,3, Cheng Y1

1Asbestos Diseases Research Institute, Sydney, Australia, 2Anatomical Pathology department, Concord Repatriation General Hospital, Sydney, Australia, 3School of Medicine, University of Sydney, NSW, Australia, Sydney, Australia, 4Sydney Cardiothoracic Surgeons, RPA Medical Centre, Sydney, NSW 2050, Australia, Sydney, Australia, 5NSW health, Australia, Sydney, Australia

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant pleural mesothelioma (MPM) is an aggressive malignancy with no effective treatment options. Poor prognosis and drug resistance are the main challenges of this deadly disease. Focal adhesion kinase (FAK) inhibitors have been shown to efficiently suppress MPM cell growth and it has been proposed that the level of E-cadherin expression could potentially play a role in FAK inhibitor resistance in MPM. However, this area remains largely unknown in MPM. In this study we utilised the large collection of MPM cells, as well as in-house established MPM cell lines to study the role of E-Cadherin and FAK inhibitor in MPM.

**Methods:** MPM patient FFPE samples (60), cell blocks from four MPM ATCC cell lines and 20 primary MPM cell lines were used for IHC analysis to study the expression of E-Cadherin. Immortilised mesothelial cells (MeT-5a) and other cancer cell lines were utilised as non-MPM controls. The mRNA expression of E-cadherin was quantified by RT-qPCR and IHC staining and a subsequent statistical analysis was performed. All cell lines were treated with FAK inhibitor (PND-1186) and drug response was analysed by Alarma-blue proliferation assay.

**Results:** Our result indicated that E-cadherin is down-regulated in MPM tissue samples. The majority of FFPE samples showed either a very low or absent expression of the E-Cadherin protein. For the tested cell lines, four MPM cell lines (H226, Ren, 2174 and 2291) showed an up-regulation of E-cadherin expression when compared to the immortalised mesothelial cell control. Additionally, E-cadherin was found to be highly expressed in other non-MPM cancer cell lines (PC9, HCC827 and MNK45). MPM cells with high E-Cadherin expression exhibited a resistance to PND-1186. Cell lines that exhibited a relative sensitivity to PND-1186 included the non-MPM cell lines, as well as the two non-E-cadherin-expressing MPM cell lines, H28 and MSTO. When comparing PND-1186 sensitivity in MPM cells only, it is sensitive if cells do not express E-cadherin however become resistant when E-cadherin is retained.

**Conclusion:** Our observation indicated that the presence of E-cadherin expression is associated with PND-1186 resistance and is highly specific in MPM cells only. For all other non-MPM cancer cell lines, E-cadherin expression did not seem to play a role in FAK inhibitor resistance.

**Keywords:** E-Cadherin, FAK inhibitor, mesothelioma, drug response

---

**P135: STAT3 Inhibitor JSI-124 Induces Autophagic Cell Death in RN5 Murine Mesothelioma Cells**

Zhang C1, Zhou J1, Wu L2, Peng C1, Cong B1, de Perrot M2, Zhao X1

1Department of Thoracic Surgery, The Second Hospital of Shandong University, Jinan, China, 2Latner Thoracic Surgery Research Laboratories, Division of Thoracic Surgery, Toronto General Hospital, University Health Network, Toronto, Canada

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant pleural mesothelioma (MPM) is an aggressive neoplasm with poor prognosis. STAT3, which functions as an oncogene, is constitutively phosphorylated and activated in MPM. Autophagic cell death has emerged recently as an important mechanism of cancer cell death. Increasing evidence has demonstrated that STAT3 plays roles in the regulation of autophagy. We are now focusing on a STAT3 inhibitor JSI-124 to evaluate the impact on autophagic cell death and anticancer activities in MPM.

**Methods:** Murine mesothelioma cell line RN5, initially developed by asbestos exposure in NF2 heterozygous mice, was cultured in PMRI 1640 medium supplemented
with 10% FBS and 100 IU/mL of penicillin, 100 μg/mL of streptomycin. The inhibitory effects of JSI-124 were determined by sulforhodamine B (SRB) cytotoxicity assay in cell culture. Apoptosis induced by JSI-124 was measured by Annexin-V/PI double staining. RN5 cells were pretreated with 3-methyladenine (2.5 mM) or chloroquine (50 μM) for 1h, and then coincubation with JSI-124 for another 24 h. Levels of protein expression were analyzed by western blot using antibodies against caspase 3, PARP, MAP1LC3B-II, p-mTOR/p-p70S6K and p-JAK2/p-STAT3. Autophagosome was observed by transmission electron microscope (TEM).

Results: JSI-124 inhibited RN5 cell proliferation in a dose- and time- dependent manner and the IC50 value at 72h was 600 nM. JSI-124 induced caspase 3/PARP-independent non-apoptotic cell death. TEM analysis demonstrated that an increased production of autophagosome in RN5 cells with treatment of JSI-124 (500 nM for 24h). Western blot showed that MAP1LC3B-II, a marker for autophagy, increased in a dose-dependent and time-dependent manner. Co-treatment with JSI-124 and 3-methyladenine for 24 h led to a decrease of JSI-124 induced MAP1LC3B-II formation, while treatment with JSI-124 and chloroquine resulted in increased conversion of MAP1LC3B-II. Inhibition of autophagy enhanced JSI-124 induced apoptosis in RN5 cells. JSI-124 decreased the level of mTOR/p70S6K and p-STAT3/p-JAK2 in a dose- and time-dependent manner. It demonstrated that mTOR/p70S6K and JAK2/STAT3 signaling was involved in JSI-124 induced autophagy in RN5 cells.

Conclusion: STAT3 inhibitor JSI-124 induces protective autophagy in RN5 murine mesothelioma cells through mTOR/p70S6K signaling pathway, suggesting that JSI-124 may be a potential therapeutic strategy for MPM.

Keywords: MPM, Autophagy, STAT3, JSI-124

P136: Malignant Pleural Mesothelioma of the Women in Our Hospital

Ando K1, Morohoshi T1, Mitsubori T1, Urata N1, Natsume I1, Fujiwara T1, Tsuura Y1

1Yokosuka Kyosai Hospital, Yokosuka, Japan

Poster Session, Virtual, May 7, 2021

Objectives: The large-scale study on gender differences of the mesothelioma was published in succession from Italy and Sweden. We analyze the cases of the mesothelioma which we experienced so far in our hospital to confirm the characteristic of the mesothelioma of the women in Japan.

Methods: We examined 12 consecutive cases of the malignant pleural mesothelioma of the women whom we treated from 2008 through 2018 in our hospital.

Results: The age at the time of the diagnosis were 51-87 years old (median 72 years old). The types of the histology were epithelioid 8, biphasic 1, desmoplastic 1, localized malignant mesothelioma 1, and well differentiated papillary mesothelioma 1, respectively. Regarding the asbestos exposure, three cases were domestic exposure and one case was environmental exposure, but the remaining 8 cases were uncertain. Among 12 cases, 5 cases underwent surgical operations: extra pleural pneumonectomy 2, pleurectomy/decortication 2, and left upper lobectomy with chest wall resection (for the localized malignant mesothelioma) 1, respectively. All of them were followed by chemotherapy. As for other 7 cases, 4 cases received only chemotherapy, and 3 cases were no treatment. The median survival time was 432 days. The cases who lived longer than three years were 4: extra pleural pneumonectomy followed by chemotherapy for epithelioid mesothelioma 2, pleurectomy/decortication 2, and left upper lobectomy with chest wall resection (for the localized malignant mesothelioma) 1, respectively. All of them were followed by chemotherapy. As for other 7 cases, 4 cases received only chemotherapy, and 3 cases were no treatment. The median survival time was 432 days. The cases who lived longer than three years were 4: extra pleural pneumonectomy followed by chemotherapy for epithelioid mesothelioma 2 (in one case, intensity modulated radiation therapy was also performed), the localized malignant mesothelioma 1, well differentiated pleural mesothelioma with no treatment 1, respectively.

Conclusion: Similar to the studies published in other countries, the fact of asbestos exposure was not clear in Japanese women who affected with malignant pleural mesothelioma. Furthermore, the prognosis of them, especially who underwent surgery, seems to be better than others.

Keywords: mesothelioma in women, Japan
P138: A Brisbane Mesothelioma Case with Worldwide Significance

Kazan S

1Kazan Mcclain Satterley Greenwood, Oakland, United States

Poster Session, Virtual, May 7, 2021

Objectives: We report a case where the manufacturer of gaskets causing asbestos exposure concealed the fact that its gaskets contained asbestos. Legal proceedings in the Brisbane case uncovered the truth.

Method: The subject is CM. Occupational asbestos exposure information was obtained through interviews and depositions. Information about product asbestos content and lack of warnings was obtained through litigation discovery.

Results: CM was born in 1951. She was diagnosed with Sarcomatoid Malignant Pleural Mesothelioma in 2016 and died in 2017.

CM worked as a mechanic at a containerized freight business in California from 1976-1982, and was responsible for maintaining the business’ vehicles and equipment. She worked with Thermo King gaskets on truck-mounted Thermo King refrigeration units, including scraping and wire-brushing these gaskets and gasket residue. None of the Thermo King gaskets were labeled or otherwise identified as containing asbestos.

CM emigrated to Australia in 1982, started her own Brisbane-based transport refrigeration repair company that she ran until her death in 2017, and worked around employees working with the same Thermo King gaskets. Again, none of these gaskets were labeled or otherwise identified as containing asbestos.

CM never saw any labels or warnings that these gaskets contained asbestos. The work histories taken by CM’s treating physician reflect CM’s lack of knowledge, noting only that she “worked in a dusty environment with machinery.”

In litigation, Thermo King admitted it sold gaskets that contained 70-90% asbestos worldwide, including in California and Australia, until 1994. Thermo King also admitted it did not provide any information or warnings to end-users that its gaskets contained asbestos or were hazardous. The case was resolved by mutual agreement.

Conclusion: CM was unknowingly exposed to asbestos through her work because Thermo King did not label or warn that its gaskets contained asbestos. Physicians should, of course, take a thorough work history of mesothelioma patients, but patient denial of asbestos exposure is to be expected when manufacturers conceal information about the asbestos content of their products. Literature based on patient history may therefore be inaccurate through no fault of the patient; “no history of asbestos exposure” is not the same as “no asbestos exposure.”

Addendum: In 2019, Trane Corp, responsible for all Thermo-King asbestos liability, completed a series of very complicated corporate transactions designed to put those liabilities into a new company, which filed for bankruptcy reorganization protection in the U.S. Bankruptcy Court in Charlotte, North Carolina on June 17, 2020, (in re Aldrich Pump LLC, et al., #20-30608), while keeping all the valuable assets in its parent and affiliate companies who remain outside of bankruptcy jurisdiction but are protected from all litigation by their asbestos victims. The author currently serves on the court appointed Asbestos Creditors’ Committee in the Aldrich Pump case.

P139: Nivolumab for Malignant Mesothelioma: A Real-world Experience


1Hyogo College Of Medicine, Nishinomiya, Japan

Poster Session, Virtual, May 7, 2021

Objectives: Nivolumab, an anti-PD-1 monoclonal antibody, has beneficial effects against pretreated malignant pleural mesothelioma (MPM). Although this drug is approved in Japan, data on the efficacy and safety of nivolumab in MPM are limited to those from a small number of patients in the MERIT study. Therefore, it is important to accumulate real-world data of nivolumab.
Methods: We retrospectively analyzed all patients with MPM who received nivolumab at Hyogo College of Medicine Hospital from August 2018 to March 2019. The tumor response was assessed according to RECIST guidelines (version 1.1), and adverse events were evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Results: A total of 65 patients (50 males and 15 females) were included. There were 52, 8, and 5 patients with a performance status of 0-1, 2, and 3, respectively. There were 54, 8, and 3 patients with epithelioid, sarcomatoid, and bi-phasic histology, respectively. Nivolumab was given as second-, third-, and ≥fourth-line treatment to 37, 15, and 13 patients, respectively.

The response rate (RR) was 21.5% (14/65), and disease control rate (DCR) was 55.4% (54/65). Nineteen patients were evaluated as progressive disease and 10 patients were not evaluable. The RR and DCR were 16.7% (9/54) and 51.9% (28/65) in the epithelioid-type, and 50.0% (4/8) and 87.5% (7/8) in the sarcomatoid-type. The median progression-free survival was 3.3 months and median overall survival was not reached. Regarding adverse events, fatigue (grade 1−2) was observed in 8, hypothyroidism (grade 1-2) in 11, renal dysfunction (grade 1-3) in 6, loss of appetite (grade 1-2) in 2, pneumonitis (grade 3) in 1, rash (grade 1) in 2 and hypopituitarism (grade 3) in 1 patients, respectively.

Conclusion: The findings of this retrospective study revealed the effectiveness and safety of nivolumab for MPM in the real-world setting. Nivolumab can be used as a standard second-line treatment for MPM.

Keywords: nivolumab, MPM


Whilst a number of cancers have benefited from drug developments, standard of care in the UK health setting for mesothelioma has not changed in over 10 years. There’s still no NHS approved second line treatment option. This has led to a lack of consensus and inequality in accessing drugs.

This collaboration considers the challenges faced by the medical and legal professions when advising patients about their treatment options and offers guidance to Lung Cancer Nurse Specialists who are often charged with having difficult discussions ahead of patients making a final decision.

Methods: The authors reviewed current medical evidence alongside patient led social media accounts of experiences of non NHS funded therapies. They also shared & discussed their vast experience of supporting patients to access treatment/trials after standard chemotherapy.

Results: Some early phase studies have shown that immunotherapy may help extend life expectancy of mesothelioma patients. More convincing evidence is needed before such treatments will be granted a licence for use in this setting in the UK. The recent results from PROMISE fail to show any survival benefit when comparing Pembrolizumab against chemotherapy. To access immunotherapy patients must either fund it privately (c.£280k – 2 years) through savings, private health insurance or litigation or by participating in clinical trials.

Clinical trials are essential to enable us to discover new treatments and new ways to detect, diagnose and reduce the risk of disease. The future of treatment relies on patients who are willing to participate in trials. However, treatment is not guaranteed. Placebo is a possibility and is currently ethically acceptable in the control arm of a trial.

Mesothelioma UK fund Regional Specialist Nurses to support local clinical teams in many areas across the UK and should always be contacted for up to date information and advice relating to clinical trials.

Patients should also be advised about the option of private treatment. It might be thought to be cruel to inform someone of a treatment which may prolong their life or...
improve their quality of life because it is beyond their means, it undermines patient autonomy not to inform them of all treatment options. Litigation relating to negligent asbestos exposure can provide a source of funds.

**Conclusion:** Whilst mesothelioma is a devastating disease clinical trials offer hope for both patients now and in relation to finding treatments for future patients.

Some patients are in the position of having more options for treatments beyond first line because they have access to funding for private treatment.

Patients/clients should be empowered to weigh up their options rationally and free from pressure.

Treating clinicians and solicitors should have an open dialogue early and work together to ensure the patient is well informed.

---

**P141: Identifying the Severity of Psychosocial Symptoms Among Patients Diagnosed with Mesothelioma. Do We Really Need Emotional Support Groups?**

**Fatima A.**

1Shaukat Khanum Cancer Hospital, Lahore, Pakistan

**Poster Session, Virtual, May 7, 2021**

Objectives: Malignant mesothelioma is a rare and fatal malignancy, associated with occupational and environmental exposure to asbestos. Most of the mesotheliomas are either misdiagnosed or diagnosed at later stages among those patients who are underprivileged. The diagnosis and treatment of mesothelioma is a continuous emotional distress for both patient and their family. We aim to identify the severity of depression, emotional distress, stress and mental fatigue among those patients who are diagnosed with mesothelioma.

**Methods:** A cross sectional study was conducted in Shaukat Khanum Hospital, Lahore from March 2017 to April 2019. Exclusion and Inclusion criteria were made. 76 were enrolled in the study. Sociodemographic characteristics were evaluated using Beck Depression Inventory and socio demographic form. Severity of depression was estimated by using Hamilton D (HAM-D). Various variables were analysed including parent’s age, level of education, socioeconomic status, gender and number of children.

**Results:** 69% of the participants exhibited severe range of depression. 25% showed moderate depression whereas 6% participants were showing the mild range of depression. An inverse co relation was found between educational status, occupational status (paid or unpaid), their marital status, socioeconomic family status and depression. Women 71% were found to be more depressed than males.

**Conclusion:** We concluded that majority of patients from psychosocial symptoms particularly depression and it is mainly associated with some factors. There is need to incorporate patients into the diagnosis and treatment process so that we can over come the effects of depression on the health outcomes of patients diagnosed with lung cancer. This can only be possible through appropriate education and emotional support programmes.

**Keywords:** mesothelioma, support groups, depression

---

**P142: Evaluation of Mesothelioma in a Large District General Hospital in the UK 2017 - 2018. A Retrospective Case Note Audit**

**Moylan A.**

1Portsmouth Hospitals University NHS Trust / Mesothelioma UK, , United Kingdom

Objectives: The United Kingdom has the highest incidence of Malignant Mesothelioma (MM) in the world. There are pockets of high incidence around the country particularly in areas with a history of ship building, military ports and highly industrialised areas. Portsmouth on the South Coast of England is one of these areas with an average of 36 patients diagnosed per year from 2013 to 2018 (range 25-53). It is the home of the Royal Navy and has a long history of military, commercial and leisure ship building.
The purpose of this audit is to evaluate the demographic, treatment and outcomes of patients diagnosed in the District General Hospital serving this area from 1st January 2017 to 31st December 2018. This period also covers the first two years tenure of a full time Mesothelioma Clinical Nurse Specialist.

**Methods:** All patients diagnosed with MM in Portsmouth from 1st January 2017 to 31st December 2018 were identified. Electronic patient records and the local Excel database was used to identify gender, histological subtype, systemic anticancer treatments (SACT) given, reasons for declining treatment and survival data. Data was analysed on 31st December 2020.

**Results:** 89 patients were diagnosed with MM within the audit period, three moved out of area and two had private health insurance and opted out of NHS care leaving a cohort of 84 patients consisting of 74 men and 10 women. 82 had pleural disease and 2 had peritoneal Mesothelioma.

Key Findings

- Age range 52 – 93
- 6 patients from the audit cohort are alive. 2 have not had any SACT to date
- 7 patients had first line treatment only systemic anticancer treatment (SACT) with Pemetrexed and Cisplatin/Carboplatin
- 12 patients had 2 - 5 lines of treatment / clinical trials
- 3 patients were randomised into the MARS 2 surgical trial
- 1 patient had Gamma Knife treatment for multiple brain metastases and radiotherapy to a spinal cord metastasis following 3 lines of SACT including an immunotherapy clinical trial
- The reasons for not having SACT were complex and included the value placed on quality of life versus potential quantity, co-morbidities, the incurable nature of MM and personal opinion based on experience of others having treatment

**Conclusion:** Portsmouth is an area in the UK with a higher than national average incidence of MM. Traditionally treatment options for MM have been limited but the increased portfolio and access to clinical trials has increased the treatment choices for patients. The decision not to have SACT is complex and multi-factorial but appears to be the right decision for some patients based on survival figures in this audit. This audit will provide a baseline for future evaluation of Mesothelioma in Portsmouth.

**Keywords:** Mesothelioma, Audit


Routley C, Moore-Gillon J, Coulson J

1British Lung Foundation, London, United Kingdom, 2St Bartholomew’s Hospital, London, United Kingdom, 3The University of Liverpool, Liverpool, United Kingdom

**Poster Session, Virtual, May 7, 2021**

**Objectives:** The British Lung Foundation (BLF) is a charity that supports people with lung disease, offering hope through research, help through support services and a voice through campaigning. Since 2002, the charity has funded more than £9.8 million (US$13.5 million) of mesothelioma research in basic, translational and clinical research fields.

The BLF’s Mesothelioma Research Network (MRN) brings together basic science researchers, clinical researchers and specialist health professionals in the field of mesothelioma to share knowledge, skills and resources. It aims to facilitate research progress and improve patient outcomes. Additionally, the MRN endeavours to increase investment in mesothelioma research.

**Methods:** The MRN was launched in October 2017. Success is measured against performance indicators including member numbers and member feedback. Members surveys were conducted in July and December 2018, July and December 2019, November 2020 and January 2021.
Results:

- Mesothelioma research supported by the BLF, the Victor Dahdaleh Foundation and underpinned by MRN infrastructure has assisted in attracting an additional £27 million (US$37 million) into mesothelioma research.
- The MRN has more than 200 members ranging from PhD students to departmental heads and includes researchers from around the world.
- The MRN hosts an online networking platform. It details members' specialist skills and resources they can share as well as their contact email. This allows members to reach out to others to get support or collaborate.
- A second UK-based MRN Research Day was attended by 104 researchers. The meeting provided key research updates and vital networking opportunities. 92% of delegates who fed back rated the programme as excellent or good and 68% said they'd made new contacts that could lead to collaborations. The next Research Day is planned for 2021.
- 4 research webinars were delivered between 2019 and 2021 on basic and clinical research in mesothelioma. These are accessible to members worldwide. The latest webinar was attended by 47 members of the MRN.
- In the November 2020 members pulse survey, 72% of responders felt that being a member of the MRN helped them in their work as a researcher and 86% would recommend being an MRN member to a colleague.
- Since its inception the MRN has enabled approximately 18 new research collaborations by connecting members of the research community. In addition, one collaborative project, to determine if mesothelioma development can be prevented with therapeutics, has been funded by MRN. A further collaborative project will be funded in BLF’s 2021 grant round.

Conclusion: In three years, the MRN has grown dramatically and now includes international, non-UK researchers. It has aided the attraction of additional funding for mesothelioma research, funded research and enabled new collaborations. The MRN has funded attendance of early career investigators at the International Mesothelioma Interest Group (iMig) meeting and will continue to fund research projects. The MRN aims to support and complement the work of other organisations, including iMig, by helping researchers to connect more easily between meetings.

We encourage researchers worldwide to join us to Share. Connect.Collaborate.

The MRN is supported by the Victor Dahdaleh Foundation.

**P144: The Survival of a Mesothelioma Support Group through the Covid 19 Pandemic: Improvise and Overcome**

Slaven K1,2, Songco J1

1Royal Papworth Hospital, Cambridge, United Kingdom, 2Mesothelioma UK, ,

Poster Session, Virtual, May 7, 2021

Objectives: Support groups for patients with cancer and those who care for them can provide valuable information and advice from experts and offer peer support at difficult times. Mesothelioma is a devastating disease that can have a high emotional impact on patients, families and carers.

The Papworth Mesothelioma Social Group (PMSG) was founded in 2008 and monthly face-to-face meetings provide education, reassurance and guidance. Inherent within the social group is support and camaraderie. Attendance has been strong with an average of 49 members per month.

In March 2020, it became evident that meetings could no longer take place as before. Covid-19 was responsible for the curtailment. In order to maintain support for patients and carers, a novel way of holding the meetings was explored.

Methods: After a hiatus of 3 months, meetings resumed in June 2020 and have continued monthly since via the virtual platform, Zoom. Each month we have a guest speaker or a quiz. Formal feedback is being sought.

Results: Attendance has reduced, however we do see regular faces returning. A small number of new patients and carers have joined.

Prior to lockdown in March 2020, the meetings would host an average of 49 people. The new format meetings have an average of 18 people.
Informal feedback from members has suggested positive factors about the on-line platform:

- Ability to join the meeting from home
- Attending the meeting when feeling fatigued and less well
- No transport concerns
- Ability to invite speakers from afar
- Ability to leave the meeting at own convenience
- Family members can participate from a distance

Negative factors reported include:

- A requirement to have access to and to understand the technology
- Non-verbal communication and cues are less obvious
- Inability to comfort people if distressed
- Difficulty in assessing emotions
- Feeling ‘exposed’ and ‘vulnerable’.

**Conclusion:** The PMSG will survive the pandemic and will resume face to face meetings as soon as it is safe to do so. The new technology will enable the group to have presentations from speakers who no longer need to be physically present at the venue.

A new way of offering support has been embraced by the group. However, all group members look towards the future when face to face meetings can take place. Feedback from the formal survey will be reported.

Support Group, Covid-19, Survival, Support, Social
P145: Mesothelioma UK - Supporting Our Armed Forces. Raising Awareness and Providing Information and Support for Veterans/Armed Forces Personnel

Wilkes H1, Booth L2, Bhayani M, Moylan A, Darlison L

1University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, 2HASAG, Southampton, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: The UK has the highest incidence of Mesothelioma in the world. As with all the population members of the UK armed forces are not spared the risk of exposure to asbestos. In 2012 the UK Government announced that fines levied against banks for manipulating the London Inter-Bank Offered rate (LIBOR) rates would be used to support Armed Forces and emergency charities. In 2016 Mesothelioma UK (MUK) applied for a grant from this scheme to support a three year project to develop a specialist service for Armed Forces personnel and veterans affected by mesothelioma – the asbestos related cancer. The aim of this study was to focus on the raising awareness and providing information and support for Veterans and Armed Forces Personnel aspect of the project.

Methods: One of this project’s four workstreams focuses on raising awareness about Mesothelioma and available support for both serving and ex-military personnel. This includes a range of media activity, utilising a variety of branded materials and the building of relationships within the Armed Forces community. The project has started this awareness campaign by:

• Developing and delivering a range of information resources to raise awareness about mesothelioma in the Armed Forces and available support.

• Creating a brand and producing branded material.

• Networking with Armed Forces Groups locally and nationally.

• Hosting Stalls and Stands at Armed Forces Events.

• Attending Armed Forces groups and clubs to engage with veterans and serving personnel.

• Continuous Media activity via film, articles, radio and social media using patient stories and interviews with the project lead Mesothelioma Nurse Specialist.

• Establishing a Facebook group for Armed Forces patients, their family and friends and anyone interested in finding out more.

• Engaging with Politicians and Local Authority Veterans Champions.

• Education and training for the charity’s Clinical Nurse Specialists, Benefits Advisor and freephone information line managers.

Results: The project team developed 4 information booklets specifically aimed at the Armed Forces community: - Mesothelioma UK’s Armed Forces Project, Asbestos and mesothelioma, Being diagnosed with Mesothelioma and Benefits and compensation.

Awareness branded goods include lapel pins, wrist bands, posters, banners, balloons and toy dog for distribution at events.

Members of the Charity’s Clinical Nurse Specialist team have attended 16 Armed Forces Events to meet members of the armed forces community.

15 media stories have been published.

A list of key stakeholders has been established and a circulation list with those interested in receiving updates about the project.

Membership of the Mesothelioma UK Armed Forces Facebook group has grown to 86 members.

Conclusion: The development of this service has been very well received by the Armed Forces community and the project continues to gather momentum, widening the range of contacts and links made. We are now rolling out a programme throughout the UK using the network of Mesothelioma UK funded mesothelioma Clinical Nurse Specialists to facilitate service delivery in their regions.
P146: Asbestos Exposure as a Cause of Well Differentiated Papillary Mesothelioma (WDPM)

Bedrossian C1, Michael C2, Maksem J3

1Biomedical Concepts, Oak Park, United States, 2University Hospitals Cleveland Medical Center, Cleveland, United States, 3Orlando Regional Medical Center, Orlando, United States

Poster Session, Virtual, May 7, 2021

Objectives: WDPM, a distinct type of mesothelioma with propensity to superficial spread without invasion, often occurs in the peritoneum of women with no history of asbestos exposure. We describe 27 cases to illustrate the occurrence of WDPM with a variable biological behavior, within and outside the peritoneum, in men as well as women, apparently exposed to asbestos, under various conditions.

Methods: Twenty seven asbestos-exposed individuals (19 women; 8 men) were diagnosed with WDPM in the period 2007-2019, based on the cyto-histological characteristics of biopsy or effusion specimens. The results were correlated with imaging studies to rule-out metastatic origin and confirmed by immuno-histochemistry in histological sections and cell blocks of fluid specimens.

Results: All but 5 cases (Pleura: 3; Tunica vaginalis: 2) occurred in the peritoneum, omentum and/or mesentery. All cases were confirmed by tissue biopsy upon VATS (2) mediastinal CNB (1), hernia repair (2); laparoscopy (16), or laparotomy (6). Cytology contained tumor cells in 14 cases (ascites: 8; pelvic washing 2; pleural fluid: 3; mediastinal FNA:1) and was interpreted as reactive mesothelial hyperplasia or atypical mesothelial proliferation. Imaging studies did not detect mass lesions, but 6 cases had pleural plaque, asbestosis, or peritoneal egg shell calcifications, suggestive of asbestos exposure. A history of exposure was positive in all cases: occupational: 6 (electrician, garage janitor, laborer, power press operator, machinist, automotive mechanic power plant); para-occupational: 3 (shade tree mechanic, 1; DIY home remodeler;2); take-home: 14 (household contacts: shade tree mechanic: 3; DIY home remodeler;2; laborer2; power plant; US Navy; maintenance; boilermaker; foundry; construction; petroleum geologist); by-stander: 3 (shopping mall and office renovations; school teacher); and one woman exposed to cosmetic talc. One case was preceded by 5 thoracentesis, three cases by multiple paracentesis prior to the diagnosis of WDPM. The cyto-histological and immuno-cytochemical profile of the tumor cells remained identifiable as mesothelial, despite the variable architecture of the lesions. Immuno-staining. Most commonly positive immunostaining reactions were the same as those of ordinary malignant epithelioid mesothelioma: Calretinin, D2-40, WT-1, HBME-1, AE1/ AE3 Keratin, CK-7 and Beta-catenin. Similar to prior examples of WDPM described in the literature, 3 cases had evidence of local invasion and 5 cases progressed to diffuse epithelioid mesothelioma. Six cases were treated with debulking cyto-reduction surgery and HIPEC. One male patient had multiple neoplasms (WDPM, prostatic carcinoma, papillary carcinoma of the thyroid). One woman each had endometriosis and Crohn's disease.

Conclusion: WDPM in asbestos-exposed individuals is morphologically and immunohistochemically indistinguishable from the same lesion described without mention of an exposure history being taken and/or with a negative history of exposure. This occurrence reinforces the biological plausibility that WDPM is a lower grade form of mesothelioma, which shares the same anatomical distribution, cell type, and in some cases the same propensity to progress, exhibited by asbestos-related diffuse mesotheliomas.

P147: Correlation of Pattern and Grade with Survival in Epithelioid Malignant Mesothelioma of the Pleura

Richards S1, Fanaroff R1, Friedberg J1, Burke A1

1University Of Maryland Medical Center, Baltimore, United States

Poster Session, Virtual, May 7, 2021

Objectives: It has been proposed that pleural epithelioid mesothelioma can be graded and categorized by architectural pattern, and that pattern and grade both affect prognosis. A three-tier grading system has been suggested, using nuclear atypia and mitotic rate to determine overall grade. Another grading scheme
incorporates the presence or absence of necrosis. The goal of this study was to determine if pattern and grade correlate with survival in patients with pleural epithelioid mesothelioma.

**Methods:** Forty-two cases of pleural epithelioid mesothelioma, diagnosed during a five year period (2014-2019), were retrospectively reviewed. Cases included 33 males and 9 females with a mean age of 64 years at diagnosis. Tumors were categorized by architectural pattern (in order of increasing aggressiveness: tubulopapillary, trabecular, solid, and micropapillary) and were evaluated both by predominant pattern and most aggressive pattern present. Cases were graded using the following criteria: nuclear atypia (1 – mild to 3 – severe) and mitotic rate (1 – 1/10 HPF; 2 – 2-4/10 HPF; and 3 – ≥ 5/10 HPF). A sum of 2 or 3 corresponded to grade I, 4 or 5 to grade II, and 6 to grade III. The presence or absence of necrosis was indicated for each case. Eight cases of biphasic mesothelioma and 2 cases of sarcomatoid mesothelioma from the same time period were included for survival comparison. Survival data was obtained and was used to create Kaplan-Meier plots. p values were calculated using the chi-square, log rank test.

**Results:** The predominant architectural pattern breakdown was: tubulopapillary – 19; solid – 15; and trabecular – 8. Seven tumors showed partial micropapillary architecture. Cases were graded as follows: grade I – 21; grade II – 16; and grade III – 5. Eleven of 42 tumors had necrosis. The Kaplan-Meier curves showed statistically significant differences in survival for most aggressive pattern present (p = 0.03) and micropapillary architecture (p = 0.005, Figure 1). The survival curve of patients with micropapillary pattern epithelioid tumors more closely resembled the curve for biphasic / sarcomatoid mesothelioma than non-micropapillary epithelioid mesothelioma. There were no significant survival differences among the other parameters tested.

**Conclusion:** There is evidence that architectural pattern has prognostic implications in epithelioid mesothelioma. The prognosis for patients with any micropapillary architecture at this institution was similar to those with biphasic / sarcomatoid mesothelioma. Given the small size of this cohort, further larger scale studies are warranted.

**Keywords:** Epithelioid, pattern, grade, prognosis

---

**P148: Is BAP-1 Immunohistochemical Expression Loss Associated with Histologic Growth Pattern In Diffuse Malignant Peritoneal Mesothelioma?**

Fanaroff R1, Ricards S1, Burke A1

1University Of Maryland Medical Center, Baltimore, United States

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Although BAP-1 expression is known to be lost in approximately half of pleural mesotheliomas, there are few studies of BAP-1 immunohistochemical staining on diffuse malignant peritoneal mesothelioma (DMPeM). This study explores BAP-1 expression in a series of DMPeM.

**Methods:** We constructed a tissue microarray of 150 cores (83 patients) from DMPeM diagnosed during a 10 year period (2006-2016) and with known histologic growth patterns. Sections of the tissue microarray were stained with BAP-1 immunostain and interpreted as staining either present (maintained expression) or absent (loss of expression).

**Results:** Of the cores stained, staining could be evaluated on 120 cores from 77 patients (80% of cores, 92% of patients). The tumors were classified histologically as well-differentiated papillary (3), multicystic (3), papillary/tubulopapillary (24), trabecular with solid or tubular areas (35), and pure solid or solid with areas of pleomorphism (12). The rates of loss of expression was 0% for well differentiated papillary and multicystic tumors, 67% for tubulopapillary, 69% for trabecular with solid or tubular areas, and 83% for pure solid tumors. The differences between rates of positivity was significant (p=.005, chi squared).
Conclusion: A high proportion of DMPeM show loss of BAP-1. There is a correlation that is statistically significant between loss of expression and decrease in differentiation.

P149: Correlation Between Reactive Fibrous Stroma in Diffuse Malignant Pleural Mesothelioma and Survival

Fananoff R1, Richards S1, Friedberg J1, Burke A1

1University Of Maryland Medical Center, Baltimore, United States

Poster Session, Virtual, May 7, 2021

Objectives: Diffuse malignant pleural mesotheliomas (DMPM) may have two types of biphasic growth pattern, one in which the spindled component is malignant, and the other in which the spindled component is reactive. A fibrous reaction to a carcinoma is termed “desmoplasia,” which would lead to confusion in mesothelioma, because of the desmoplastic subtype or pure sarcomatoid DMPM. The prognostic significance of a reactive fibrous stroma (RFS) in DMPM is unknown.

Methods: We studied 52 malignant mesotheliomas in which a surgical excision (n= 6) or extended pleural decortication (n=46) was performed. The tumors were classified as uniphasic epithelioid (UE), epithelioid with RFS, biphasic DMPM, and sarcomatoid DMPM. Survival was compared among three groups: UE, RFS and any sarcomatoid component (Sarc) using Kaplan-Meier with chi-squared/log-rank tests.

Results: There were 12 women and 40 men, with a mean age of 65 at the time of diagnosis. There were 25 UE, 11 epithelioid DMPM with a RFS, 13 biphasic DMPM, and 3 sarcomatoid DMPM. The RFP contained fibroblasts in a myxoid stroma (n=1), loose fibrous stroma (n=8) and dense fibrous stroma (n=2). In all cases the RFS was present in close association with epithelioid elements. The biphasic DMPM had separate large areas of sarcomatoid growth that were unequivocal; in two cases they were admixed with epithelial components and were confirmed malignant by BAP-1, cytokeratin, and GATA3 immunostaining. Survival data among the three groups are demonstrated in the figure.

Conclusion: In this study, RFS was associated with decreased survival and showed prognosis intermediate between that seen in uniphasic epithelioid mesothelioma and that seen in mesothelioma with sarcomatoid elements. This small study indicates that regular reporting of RFS may be useful in guiding treatment decisions in the future.

P150: How Does the Histology of Pleural Mesothelioma Evolve Over Time?

Fananoff R1, Richards S1, Burke A1

1University Of Maryland, Baltimore, United States

Poster Session, Virtual, May 7, 2021

Objectives: The determination of the proportion of sarcomatoid growth pattern in diffuse malignant pleural mesothelioma (DMPM) is important in guiding therapy and enrolment in clinical trials. There are few data comparing sarcomatoid components in biopsies vs. resections, and in resections vs. recurrences.

Methods: We studied pathologic material from 43 patients (8 women, 35 men) with DMPM in whom tissue samples acquired from at least two different time points were obtained. The chronologic sampling included biopsy and subsequent extended pleural decortication (n=25); initial biopsy and biopsy of recurrence (n=7); biopsy, EPD and subsequent recurrence (n=11). The recurrent sites included chest wall (7), peritoneum (3), pericardium (1), lung (1), gastroesophageal junction (1), brain (1), and lung (1).
**Results:** The histologic pairings were epithelial to epithelial subtypes (24); biphasic to biphasic (8) epithelioid to biphasic (6), and biphasic to pure sarcomatoid (2). In those cases of biphasic – biphasic pairings, the proportion of sarcomatoid increased in 4 cases (mean 24%) and decreased in 4 cases (mean 35%). The mean proportion of sarcomatoid in the second tissue sampling of the epithelioid - biphasic pairings was 42%. The dominant epithelioid pattern in these 6 cases was solid with transitional areas (1), solid (1) papillary (1), tubular (1), and tubulopapillary (2). The proportion of sarcomatoid in the initial sampling of the biphasic – sarcomatoid pairing was 65%. Of the 36 patients with EPD, 7 (19%) had recurrence at the biopsy site which was sampled at the time of surgery; none of these demonstrated change in histologic subtype. Six patients with EPD had prior systemic chemotherapy; 2 demonstrated significant treatment effect (75% or greater) and 4 demonstrate no demonstrable treatment effect. In one of these cases without histologic treatment effect, the histologic pattern changed from epithelioid to biphasic.

**Conclusion:** We conclude that mesothelioma changes from epithelioid to biphasic in a minority of cases (in our series, 15%), whether due to sampling or tumor progression, and that the proportion of sarcomatoid does not appear to fluctuate significantly in patients with biphasic disease.

**P151: The Prevalence of Non-Mesothelial Neoplasm in Patient With Malignant Mesothelioma – A Retrospective Analysis of 484 Cases**

**Chan C**, Prabhakaran S, Klebe S

*Flinders University, Bedford Park, Australia*

**Poster Session, Virtual, May 7, 2021**

**Objectives:** To assess the prevalence and types of non-mesothelial neoplasms in malignant mesothelioma (MM) patients.

**Methods:** Retrospective analysis of a local, clinically annotated database containing 484 cases of pleural and peritoneal MM.

**Results:** Seventy-six non-mesothelial neoplasms were identified in 61 patients with MM (12.6% of the study population with MM). Of these 61 patients, 45 (73.8%) were male and 16 (26.2%) female. Of the 42 patients with information on asbestos exposure, 40 patients (95.2%) had exposure to asbestos. One patient had four additional neoplasms, two had 3 additional neoplasms, eight had two additional neoplasms and the remaining patients had 1 additional neoplasm each. Prostate carcinoma was the most common malignancy, accounting for 17 neoplasms (22.4%) followed by breast carcinoma (10 cases, 13.2%), Renal cell carcinoma (5 cases, 6.6%) Melanoma (4 cases, 5.3%), bowel cancer and squamous cell carcinoma of skin (3 cases, 4%) , basal cell carcinoma of skin, urothelial and gastric carcinoma and astrocytic malignancy (2 cases each) with solitary fibrous tumours, desmoid, GIST, leiomyosarcoma, lung carcinoma, undifferentiated urothelial tumour, lung carcinoma, dysplastic naevus, melanoma, Non-Hodgkin lymphoma, ovarian carcinoma, soft tissue sarcoma, thyroid carcinoma, vulva squamous cell carcinoma and Wilms tumour accounting for 1 case each. The interval from the diagnosis of first neoplasms to mesothelioma ranged from 52 years to synchronous with the mesothelioma diagnosis. Only one patient received a diagnosis of malignancy (breast cancer) after mesothelioma diagnosis. A history of radiation therapy was present in 4 patients. In three of these the field of radiation included the site of mesothelioma and latency was >10 years. A positive smoking history was present in eight patients, with no information on smoking status for 44 patients. We have data on BAP 1 status for 27 out of the 61 cases. There was BAP1 loss by immunohistochemistry in 16/27 MM cases with reported BAP1 status, including 1/5 cases with additional neoplasm of melanoma and 2/5 cases of Renal cell carcinoma. BAP1 germline status was unknown for all patients.

**Conclusion:** Individuals with MM not uncommonly have second malignancies. Prostate and breast carcinoma had the highest prevalence, but not more prevalent than in the general population. Surprisingly, there was no increased prevalence of lung carcinoma in this cohort, given the aetiological association with asbestos exposure. Radiation has been proposed as contributory to mesothelioma development and may have been a risk factor in some of the patients. Whilst BAP germline status is unknown, we note an increased prevalence of some of the malignancies associated with this syndrome, e.g. renal cell carcinoma.
P152: Analysis of Recurrence of Surgically Resected Malignant Pleural Mesothelioma

Lopes A1, Manca P1, Scilla K1, Li A1, Mohindra P1, Culligan M1, Khashab T1, Glass E1, Mehra R1, Rolfo C1, Friedberg J1

1University of Maryland Medical Center - Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, United States

Poster Session, Virtual, May 7, 2021

Objectives: Malignant pleural mesothelioma (MPM) has a poor prognosis. Even localized MPM treated with maximal surgical cytoreduction in the context of multimodality treatment with chemotherapy and/or postoperative radiation therapy has been associated with recurrence, either locally and/or distantly. The goal of this study is to describe recurrence patterns and its management within a mesothelioma multidisciplinary team.

Methods: We conducted a single institution retrospective study evaluating MPM patients who underwent surgical resection followed by adjuvant therapy. Patients’ demographic information, clinical history, and surgical pathology were collected via review of medical records after IRB approval. Chi-square test was used to compare categorical variables. Survival analysis was performed using Kaplan-Meier method and Cox regression model, with calculation of disease-free survival (DFS), overall survival (OS) and post-recurrence survival (PRS).

Results: From March 2015 to August 2019, 47 MPM patients underwent surgery and 45 patients were eligible for this study. All patients were treated with extended pleurectomy/decortication (EPD) and the median follow-up was 18.4 months (range 2.8-59.5). Median DFS was 9.8 months (95%CI 7.7 -11.9), median OS was not reached, with an estimated OS at 12 months of 81.3% and median PRS was 10.9 months (95%CI 0-39.9). OS was correlated with histotype, with epithelioid cancers having a higher chance of survival (HR: 4.18, CI: 1.29 – 13.55; p=0.0098).

Twenty-nine patients experienced recurrence (64.4%): local recurrence (n=18, 40.0 %), distant recurrence (n=1, 2.2%) and local/distant recurrence (n=9, 20.0 %). Distant recurrences were most often metastases to the abdominal wall, intra-abdominal lymph nodes or peritoneal carcinomatosis. No statistical differences were observed between patients with and without recurrence (Table 1).

At recurrence, 14 patients were re-biopsied and a histological transformation was seen in three patients: epithelioid to biphasic (n=2) and biphasic to epithelioid (n=1). After recurrence, patients were treated mostly with systemic therapy alone (n=7), followed by a multimodality approach (n=6), best supportive care (n=5), radiation therapy (n=4) and surgery (n=3). After recurrence, first line systemic treatment was chemotherapy with carboplatin and pemetrexed (n=6), immunotherapy (n=4) or investigational agent on a clinical trial (n=1).

Conclusion: These results may suggest that, although recurrence is frequent in MPM, close surveillance and treatment upon detection of recurrence including multimodality approaches are important to improve OS and PRS. Sample size and retrospective nature of the analysis can be a bias of this study.
Table 1: Baseline characteristics of MPM Surgical Patients and characterization of neoadjuvant and/or adjuvant treatments (n=45).

<table>
<thead>
<tr>
<th></th>
<th>No recurrence (n=16)</th>
<th>Recurrence (n=29)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old) Median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender [n (%)]</td>
<td>Male 11 (68.8 %)</td>
<td>24 (82.8 %)</td>
<td>0.279</td>
</tr>
<tr>
<td></td>
<td>Female 5 (31.2 %)</td>
<td>5 (17.2 %)</td>
<td></td>
</tr>
<tr>
<td>ECOG [n (%)]</td>
<td>0 16 (100 %)</td>
<td>23 (79.3 %)</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>1 0</td>
<td>6 (20.7 %)</td>
<td></td>
</tr>
<tr>
<td>Smoking history [n (%)]</td>
<td>Never smoker 11 (68.8 %)</td>
<td>17 (58.6 %)</td>
<td>0.502</td>
</tr>
<tr>
<td></td>
<td>Active or former smoker 5 (31.2 %)</td>
<td>12 (41.4 %)</td>
<td></td>
</tr>
<tr>
<td>Asbestos exposure [n (%)]</td>
<td>Yes 8 (50.0 %)</td>
<td>18 (62.1 %)</td>
<td>0.433</td>
</tr>
<tr>
<td></td>
<td>No 8 (50.0 %)</td>
<td>11 (37.9 %)</td>
<td></td>
</tr>
<tr>
<td>Histology [n (%)]</td>
<td>Epithelioid 14 (87.5 %)</td>
<td>22 (75.9 %)</td>
<td>0.573</td>
</tr>
<tr>
<td></td>
<td>Biphasic 2 (12.5 %)</td>
<td>6 (20.7 %)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sarcomatoid 0</td>
<td>1 (3.4 %)</td>
<td></td>
</tr>
<tr>
<td>Pathological Stage [n (%)]</td>
<td>Stage I 10 (62.5 %)</td>
<td>9 (31.0 %)</td>
<td>0.215</td>
</tr>
<tr>
<td></td>
<td>Stage II 1 (6.3 %)</td>
<td>4 (13.8 %)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage III 5 (31.2 %)</td>
<td>15 (51.7 %)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N/A 0</td>
<td>1 (3.4 %)</td>
<td></td>
</tr>
<tr>
<td>Pericardial resection [n (%)]</td>
<td>Yes 4 (25.0 %)</td>
<td>13 (44.8 %)</td>
<td>0.189</td>
</tr>
<tr>
<td></td>
<td>No 12 (75.0 %)</td>
<td>16 (55.2 %)</td>
<td></td>
</tr>
<tr>
<td>Diaphragm resection [n (%)]</td>
<td>Yes 12 (75.0 %)</td>
<td>22 (75.9 %)</td>
<td>0.949</td>
</tr>
<tr>
<td></td>
<td>No 4 (25.0 %)</td>
<td>7 (24.1 %)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy [n (%)]</td>
<td>Neoadjuvant 2 (12.5 %)</td>
<td>6 (20.7 %)</td>
<td>0.316</td>
</tr>
<tr>
<td></td>
<td>Adjuvant 10 (62.5 %)</td>
<td>20 (69.0 %)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neoadjuvant + Adjuvant 0</td>
<td>1 (3.4 %)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No treatment 4 (25.0 %)</td>
<td>2 (6.9 %)</td>
<td></td>
</tr>
<tr>
<td>Number of cycles of chemotherapy</td>
<td>&lt; 4 cycles 2 (12.5 %)</td>
<td>4 (13.8 %)</td>
<td>0.390</td>
</tr>
<tr>
<td></td>
<td>4 cycles 7 (43.8 %)</td>
<td>15 (51.7 %)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 or 6 cycles 3 (18.8 %)</td>
<td>8 (27.6 %)</td>
<td></td>
</tr>
<tr>
<td>Platinum doublet [n (%)]</td>
<td>Cisplatin 5 (31.3 %)</td>
<td>10 (34.5 %)</td>
<td>0.224</td>
</tr>
<tr>
<td></td>
<td>Carboplatin 7 (43.8 %)</td>
<td>17 (58.6 %)</td>
<td></td>
</tr>
<tr>
<td>Anti-angiogenic treatment [n (%)]</td>
<td>Yes 0</td>
<td>3 (10.3 %)</td>
<td>0.183</td>
</tr>
<tr>
<td></td>
<td>No 16 (100 %)</td>
<td>26 (89.7 %)</td>
<td></td>
</tr>
<tr>
<td>Immunotherapy [n (%)]</td>
<td>Yes 1 (6.3 %)</td>
<td>1 (3.4 %)</td>
<td>0.662</td>
</tr>
<tr>
<td></td>
<td>No 15 (93.7 %)</td>
<td>28 (96.6 %)</td>
<td></td>
</tr>
<tr>
<td>Intra-operative treatment [n (%)]</td>
<td>Povidone-iodine 15 (93.7 %)</td>
<td>28 (96.6 %)</td>
<td>0.662</td>
</tr>
<tr>
<td></td>
<td>Peroxide 1 (6.3 %)</td>
<td>1 (3.4 %)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant radiation therapy [n (%)]</td>
<td>Port-site radiation 3 (18.8 %)</td>
<td>3 (10.3 %)</td>
<td>0.248</td>
</tr>
<tr>
<td></td>
<td>Whole pleural proton 0</td>
<td>4 (13.8 %)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No 13 (81.2 %)</td>
<td>22 (75.9 %)</td>
<td></td>
</tr>
</tbody>
</table>
P153: Guidelines for Pathological Diagnosis of Malignant Mesothelioma: 2021 Update

Husain A

1University Of Chicago, Chicago, United States

Poster Session, Virtual, May 7, 2021

Objectives: Malignant mesothelioma (MM) is an uncommon tumor that may be difficult to diagnose. The International Mesothelioma Interest Group has been writing guidelines for pathological diagnosis that are periodically updated (last one was in 2017). This is the preliminary report of the updates being considered for publication in 2021.

Methods: The guidelines are being updated based on published literature in the last 4 years, and the experience of more than 20 leading international pathologists in the field who will be co-authors. Updates were discussed by attendees of the Working Group for Multidisciplinary Classification of MM (Lyon, France, July 2018), Pulmonary Pathology Society Biennial Meeting (Dubrovnik, Croatia, June 2019) and International Mesothelioma Panel meeting (Washington, DC, March 2020).

Results: The following 9 areas have updates since the 2017 guidelines. 1) Benign versus malignant: current strategies include use of immunohistochemical (IHC) stains for BAP-1, MTAP and 5hmC followed by FISH for homozygous deletion (HD) of p16 if needed; 2) Mesothelioma in situ: recently described criteria for this diagnosis include BAP-1 loss by IHC stain and p16 HD; 3) Epithelioid MM: histological subtyping is recommended which would be prognostically useful; 4) Epithelioid MM: grading is recommended since it is prognostically important; 5) Biphasic MM: diagnostic markers to include BAP-1 loss, MTAP loss or 5hmC loss in sarcomatoid component, although discrepant cases are described; 6) Sarcomatoid MM: GATA3 IHC is useful in distinguishing from sarcomatoid carcinoma; 7) Transitional MM: this pattern has been recently better defined and shown to have a very poor prognosis, similar to sarcomatoid MM; 8) New markers and therapeutic targets include HEG-1 and PD-L1 and 9) Molecular testing of the tumor is very useful for diagnosis since several recurring somatic alterations (e.g. in BAP-1and NF2) have been described in MM. Germline testing can be performed in selected cases.

Conclusion: Morphology and IHC stain panels are still essential in the diagnosis of MM. In addition, the above recommendations are being considered for the 2021 update in guidelines for pathologic diagnosis of MM the most significant of which are subtyping and grading of epithelioid MM and use of molecular testing.

Pathologic prognostic factors; subtyping and grading epithelioid mesothelioma

P155: BAP1 and MTAP in Cytology from Effusions Versus Biopsy in Malignant Mesothelioma Diagnosis; Equally Good?

Lynggård L1, Meristoudis C1, Panou V2,3,4, Vyberg M1,3, Reel Q1,5,6,7

1Institute of Pathology, Aalborg University Hospital, Aalborg, Denmark, 2Dept. Of Respiratory Medicine, Odense University Hospital, Odense, Denmark, 3The Clinical Institute, Aalborg University, Aalborg, Denmark, 4Clinical Cancer Research Center, Aalborg University Hospital, Aalborg, Denmark, 5Department of Oncology, Aalborg University Hospital, Aalborg, Denmark, 6Cancer Clinic, Levanger Hospital, Nord-Trøndelag Hospital Trust, , Norway, 7Department of Clinical Research and Molecular Medicine, Norwegian University of Science and Technology, Norway

Poster Session, Virtual, May 7, 2021

Objectives: Recurrent serous effusion is often the first symptom of malignant mesothelioma (MM). The diagnosis of MM on cytological material remains controversial. Therefore a complementary biopsy is almost always needed. Comorbidities and other clinical factors may be hurdles in obtaining representative tissue for diagnosis. Obtaining pleural effusion for cytology is a minimal invasive procedure that most patients can endure, and provided that a definitive diagnosis is set, an earlier treatment can be initiated.

Loss of BRCA1-associated protein (BAP1) in combination with loss of methylthionadenosine phosphorylase (MTAP) detected by immunohistochemistry (IHC), has showed to be reliable markers in the diagnosis of malignant pleural
mesothelioma (MPM) on histological sections.

In this study we aimed to investigate the BAP1 and MTAP expression in a cohort of MM patients based on cytology effusions compared to histologic sections.

**Methods:** Histological and cytological material from the available cellblock was obtained from a cohort of MM patients from Aalborg University Hospital, Denmark during the period 1977-2013, and was used to construct a tissue microarray (TMA). A normal paraffin block section was used from patients with confirmed reactive mesothelial proliferations (RMP).

The sections were incubated with respectively monoclonal antibody MTAP (ABcam; 1:2000 dilution, RT 32 min) and monoclonal antibody BAP1 (Santa Cruz Biotechnology; 1:50 dilution; RT 32 min). The immunostaining was carried out using Ventana Benchmark Ultra stainer (Roche).

The MM re-evaluation and confirmation, as well as the interpretation of the immunohistochemical (IHC) labelling of the biopsy specimens was performed by two pathologists. The three TMA punches from the same patient were evaluated altogether and assigned a single score of retained or lost expression.

**Results:** A total of 162 MM (156 pleural, 6 peritoneal), 76 cytological, 86 histological (31 bifasic, 39 epithelioid, 16 sarcomatoid) and 20 RMP histological samples were included in the study.

The combination of BAP1 and MTAP differentiated MM from RMP with a 100% specificity and sensitivities of 59% in effusion cytology and 61% in histologic sections. In discrimination of sarcomatoid MM from RMP the sensitivity was 50%, biphasic MM from RMP 76.5%, and epithelioid MM from RMP 53.9%.

BAP1 and MTAP alone showed a sensitivity of 69.7% and 42.1% in cytology, and 54.7% and 43% respectively in histology. 51(31.5%) cases showed loss of expression for both markers, 26(34.2%) and 25(29.1%) in cytology and histology respectively. In 34(21%) samples, 18(23.7%) cytological and 16(18.6%) histological, the expression was retained for both. 128(79%) demonstrated loss of expression for at least one marker, 58(76.3%) for cytology, 70(81.4%) for histology. No sarcomatoid component was morphologically identified in the cytological material.

**Conclusion:** Combination of BAP1 and MTAP as biomarkers for differentiating MM from RMP in cytology samples, is as reliable as in histology sections. However, it must be taken into consideration that the sarcomatoid component is not represented in effusion cytology

**P156: Tumor Vimentin Expression as a Prognostic Factor in Malignant Pleural Mesothelioma**

**Nasser A¹, Baird A¹, Saint-Pierre M², Laurie S¹, Wheatley-Price P¹**

¹The Ottawa Hospital/University of Ottawa, Ottawa, Canada, ²Montfort Hospital/Division of Respiratory, University of Ottawa, Ottawa, Canada

**Poster Session, Virtual, May 7, 2021**

Objectives: Vimentin is an intermediate filament protein whose expression has been associated with poor prognosis in several malignancies, such as non-small-cell lung carcinoma (NSCLC), hepatocellular carcinoma, and breast cancer. Prognostic factors in malignant pleural mesothelioma (MPM) have been previously described by groups such as EORTC and CALGB, but the role of vimentin in MPM has not been described. The aim of this study was to evaluate the prognostic value of vimentin expression in MPM.

**Methods:** With ethics approval, we collected and analyzed demographic, diagnostic, treatment and survival data on all patients with MPM treated at The Ottawa Hospital Cancer Centre between January 1991 and March 2019.

**Results:** In total 337 patients were included in the study, 95 of whom had known vimentin staining status. Vimentin was positive in 79 patients, negative in 16 patients, and unknown in 242. Characteristics of each group are provided in table 1, and survival curves in figure 1.
Sarcomatoid or biphasic histology accounted for 35% of the vimentin positive group, compared to only 6% of the vimentin negative group, and 19% of the vimentin unknown group. Median overall survival (OS) in the vimentin positive and negative groups were 6.51 and 14 months (p=0.009), respectively, compared to 10.8 months in the vimentin unknown cohort. To account for the higher frequency of non-epithelioid histology in the vimentin positive group, survival was reported just among the epithelioid subtype: OS for positive and negative vimentin was 7.56 and 12.7 months (p=0.049), respectively.

**Conclusion:** While the numbers in this study are relatively small, vimentin staining may be a significant negative prognostic factor, even when controlling for histological subtype. Further investigation is required.
**P157: Isolation of Cytotoxic Compounds Against Mesothelioma Cells from Epicoccum Nigrum, an Endophyte Isolated from Ferula Sumbul Plant**

**Perveen I**, Raza A, Ahmed S

1Microbiology Research Laboratory, Department of Microbiology, Quaid-i-Azam University, Islamabad, Pakistan, 2Department of Chemistry, University of Gujrat, Gujrat, Pakistan

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Owing to the importance of endophytes for the production of biologically active secondary metabolites, current research establishes the chemical characteristics of the cytotoxic compounds (active against mesothelioma cells) of Epicoccum nigrum isolated from Ferula sumbul plant.

**Methods:** In the course of work aimed at the discovery of new cytotoxic compounds from endophytes of medicinal plant, Ferula sumbal, a lipophilic extract of the endophyte Epicoccum nigrum displayed significant cytotoxicity against human mesothelioma cell lines, NCI-H226 (ATCC CRL-5826). Bioassay-directed fractionation of this extract followed by LC-MS/MS resulted in the isolation of important compounds including some prodiginines.

**Results:** This study reveals the potential of Epicoccum nigrum as an important source of colored, cytotoxic compounds. Prodigiones is a large family of pigmented oligopyrrole antibiotics. Prodigiones are of potent clinical interest because they are reported to have anti fungal, anti bacterial, anti protozoal, anti malarial, immunosuppressive and anti cancer activities. This is the first report of isolation of prodiginines from Epicoccum nigrum.

**Conclusion:** In conclusion, assays in current research using the crude extract and fractions of secondary metabolites of Epicoccum nigrum showed a significant cytotoxic activity against mesothelioma cells.

Thus strain could be further exploited for various applications in pharmaceutical, for its secondary metabolites.

**Keywords:** Anti-mesothelioma activity, endophytic extract, bioactive compounds, prodiginines

**P158: Histological Analysis of Asbestos-exposed MexTAg Mice**


1The National Centre of Asbestos Related Diseases (NCARD), Perth, Australia, 2School of Medicine, The University of Western Australia, Perth, Australia, 3School of Biomedical Science, The University of Western Australia, Perth, Australia, 4Department of Anatomical Pathology, Pathwest Laboratory Medicine, Perth, Australia

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Asbestos is a group of six naturally occurring, long, thin mineral fibres that are known to induce asbestos-related diseases (ARD) including asbestosis, pleural plaques and mesothelioma. Additionally, there are other non-asbestos mineral fibres with similar structural and pathogenic properties, known as asbestiform fibres (i.e. erionite). We used the MexTAg model, a well characterised mouse model that develops ARD only after exposure to asbestos fibres, to analyse tissue changes induced by several geographically distinct asbestos and asbestiform fibres.

**Objectives are:**

To perform comprehensive histological analyses on tissue samples from MexTAg mice exposed to different asbestos and asbestiform fibres.

To elucidate whether the incidence of ARD is influenced by fibre type, with the goal to generate a relative ‘carcinogenic index’ to better identify the relative risk of developing ARD.

**Methods:** MexTAg mice (30/group) were exposed to either crocidolite, amosite, chrysotile or erionite and monitored for overall survival, latency and progression. At a predefined endpoint, mice were euthanised and histological analysis performed on macroscopic tumours and organs including spleen, liver, kidney and diaphragm. Evidence of ARD included mesothelial thickening, tumours, cell atypia, necrosis, immune infiltrates, and presence of asbestos fibres relative to age matched, non asbestos exposed controls.

**Results:** All fibre-exposed mice had significantly more microscopic tumours (p<0.0001) and mesothelial thickening (p<0.05) compared to non-exposed controls. All asbestos
and asbestiform fibre groups exhibited very high prevalence of mesothelial thickening (range 96.4% to 100%).

When comparing between fibre exposed groups, we observed significantly less microscopic tumour in the erionite group (74.1%) compared to short-fibre chrysotile (100%, p<0.01); intermediate fibre chrysotile (95.5%, p<0.05), or Wittenoom crocidolite fibres (100%, p<0.05). No significant differences were observed between erionite relative to amosite (86.7%), Rhodesian chrysotile (92.9%), or Johannesburg (92.9%) or IUCC (90.0%) crocidolite.

No significant difference was observed in the proportion of mice with microscopic tumours between the different asbestos fibre groups, except for chrysotile short fibres, which induced significantly more microscopic tumours than amosite fibres (100% vs. 86.7%, p<0.05).

Conclusion: All fibre exposed MexTAg mice displayed high prevalence of mesothelial thickening and microscopic tumours, indicating that different serpentine and amphibole fibres induce similar ARD related pathologies in vivo. Furthermore, the asbestiform fibre erionite, also induced histological evidence of ARD, albeit less prevalent in comparison to some, but not all asbestos fibre groups. Data analysis is ongoing for other histological parameters and a full analysis will be reported at iMig 2020.

**P159: Mesobank UK – A Globally Available Bioresource for Malignant Pleural Mesothelioma**

**Rintoul R**¹, **Rassl D**², **Meakins S**², **Marciniak S**¹

¹University Of Cambridge, UK, Cambridge, United Kingdom, ²Royal Papworth Hospital, UK, Cambridge, United Kingdom

**Poster Session, Virtual, May 7, 2021**

Objectives: MesobanK UK was set up in 2014 to provide the research community with well-annotated, quality controlled biospecimens from patients with malignant pleural mesothelioma (MPM).

Methods: MesobanK comprises a) prospectively collected fresh tissue, b) cell lines and c) a tissue microarray from 800 cases of MPM.

Patients with suspected or confirmed MPM undergoing routine diagnostic or treatment procedures donate up to 5 tumour samples collected into RNALater™, whole blood, plasma, serum and pleural fluid. Through collaboration with Dr Marion MacFarlane, Leicester and Dr Zsuzanna Tabi, Cardiff, MesobanK is distributing 22 cell lines, all of which have been STR profiled.

The TMA has been constructed from formalin fixed paraffin embedded blocks with high quality anonymised-linked clinical data from cases diagnosed in hospitals across the UK in the last 10 years. A minimum of 4 cores is taken from each block to allow for tumour heterogeneity. TMA sections are scanned into a digital pathology imaging system to facilitate scoring.

A bespoke database has been constructed to collect anonymised-linked clinical data on all prospective and retrospective cases. Baseline data is supplemented by longitudinal data downloads on subsequent treatment episodes and survival from Public Health England National Cancer Registration and Analysis Service.

A radiology database of available imaging on each case is being constructed in order to allow clinicopathological radiological correlation.

Research groups are encouraged to make their data publically available in order to enrich data holdings on cell lines and TMAs.

Results: Since 2014, 653 patients from 14 sites have been recruited to MesobanK, of whom 600 have donated samples of some type. To date, 553 patients have donated 2610 pleural samples (with matched whole blood, serum and plasma) and 381/600 patients with pleural effusions present, have donated pleural fluid and cell pellets. Because many of the recruited cases are suspected mesothelioma, we have found that 68% of donors have a final diagnosis of MPM, the remainder being non-malignant (mainly benign reactive pleuritis). By histology, 65% of the MPM cases are epithelioid subtype, the remainder being divided between biphasic and sarcomatoid subtypes.

With regard to tumour nuclei content 30% of MPM samples contained ≤5% tumour nuclei; 36%, 5-25%; 16%, 26-50%; 10%, 50-75% and 8% >75% tumour nuclei. The bias towards low tumour nuclei composition reflects the high stromal content of MPM specimens. Tumour necrosis levels are low - 87% of samples reviewed containing no necrosis.
To date MesobanK has supplied tissue, cell lines or TMA sections with associated data to 38 academic or pharma research groups within and outwith the UK. Thirteen groups have requested subsequent specimens.

**Conclusion:** MesobanK provides high quality well annotated biospecimens which are proving popular among academic and pharma research groups. In addition, three research groups are working with MesobanK to collect bespoke project-specific specimens using the MesobanK infrastructure.

More details are available at www.mesobank.com

MesobanK thank all the patients who have donated samples and data.

MesobanK is funded by the Victor Phillip Dahdaleh Charitable Foundation through the British Lung Foundation.

Malignant Pleural Mesothelioma; tissue banking; tissue microarray; cell lines

---

**P160: Expression of Glucocorticoid and Androgen Receptors in Malignant Mesothelioma (MM)**

Schulte J¹, Husain A¹, Kindler H¹, Conzen S²

¹The University Of Chicago, Chicago, United States,
²University of Texas Southwestern Medical Center, Dallas, United States

**Poster Session, Virtual, May 7, 2021**

Objectives: Emerging evidence suggests an important role for cellular signaling through the glucocorticoid receptor (GR) in several malignancies. Depending on cancer subtype, activation of GR may either slow cell proliferation or inhibit cell death by chemotherapy. High tumor cell GR expression may also predict risk of progression. GR and the related androgen receptor (AR), can both be targeted by receptor agonists or antagonists. To date, GR and AR have not been extensively studied in MM. GAS5, a GR decoy, is often deleted in MM. Silencing of GAS5 has been shown to induce GR-regulated genes. Given emerging evidence suggesting a role for targeted therapy against these receptors in other tumor types, this study sought to define GR and AR expression by immunohistochemistry (IHC) in MM.

**Methods:** MM cases were identified from the pathology archives and foci of tumor were identified for creation of 5 tissue microarrays (TMA). TMAs were tested by IHC using anti-GR and anti-AR antibodies. GR and AR expression was recorded as percent of tumor cells positive and qualified as weak, moderate, or strong expression. For biphasic MM, the percent and intensity of expression was recorded in both the epithelioid and sarcomatoid components.

**Results:** Eighty cases of MM were scored for GR and AR from the 5 TMAs: 12 epithelioid peritoneal MM, 25 biphasic pleural MM, and 43 epithelioid pleural MM. Among these 80 cases, 96% demonstrated GR expression in greater than 10% of tumor cells; 11% showed AR expression in greater than 10% of tumor cells. Looking specifically at epithelioid MM (both peritoneal and pleural), 95% of the 55 cases showed GR expression ranging from 10% to >95% (median: 70% expression; mode: 80%). Only 2 epithelioid cases were negative for GR (0% expression) and 1 had <10% expression. AR expression >10% was observed in 13% of the 55 epithelioid MM; 1 case had 30% expression, the remaining 6 had 10% expression; 25% of the epithelial MM had AR expression between 0 and 10%. In the 25 cases of biphasic MM, 92% showed positivity for GR with a median of 50% expression and mode of 20% in the epithelioid components compared with a median of 70% expression and mode of 80% in the sarcomatoid components. Sarcomatoid components showed greater GR expression than the epithelioid components (p=0.015). AR was positive in 2 cases of biphasic MM; 1 with 10% positivity in the epithelioid component only, and the other with 10% positivity in the sarcomatoid component only. Among the cases with GR expression, 76% showed moderate to strong intensity. AR showed weak intensity among all cases with expression.

**Conclusion:** GR is moderately to strongly expressed in the majority of epithelioid and biphasic MM. In contrast, AR shows only weak expression in a small number of cases. GR expression and its downstream gene expression could be a potential therapeutic target in MM.
P161: A Case of Malignant Pleural Mesothelioma Thought to Have Developed in Bilateral Pleural Cavities

Tsujimura T1, Yuki M1, Sumida A1, Shinohara Y1, Sato A1

1Hyogo College of Medicine, Nishinomiya, Japan

Poster Session, Virtual, May 7, 2021

Objectives: Malignant pleural mesothelioma (MPM) is thought to develop from the parietal pleura in association with asbestos exposure. Even if MPM is present in both pleural cavities, it is usually explained that MPM developed from the unilateral parietal pleura has spread to the contralateral pleural cavity. Recently, it has been reported that a combination of methylthioadenosine phosphorylase (MTAP) and BRCA1-associated protein 1 (BAP1) immunohistochemistry (IHC) is useful method for differentiating MPM cells from reactive mesothelial cells. Here, we present a case with MPM thought to have developed bilaterally by examining BAP1 and MTAP expression.

Methods: We examined BAP1 expression in the cellular nuclei and MTAP expression in the cytoplasm in pleural biopsy specimens of a patient with MPM by IHC.

Results: A man in his 50s visited our hospital complaining of respiratory distress during work. Chest CT image showed bilateral pleural effusion and pneumothorax in the left lung. Pleural effusion cytology showed atypical mesothelial cells in the right pleural effusion, suggesting that they were MPM cells. Right pleural biopsy showed that calretinin-positive and D2-40-positive atypical cells were proliferated in the right parietal pleura and invaded into the stroma. Since atypical cells were BAP1-negative and MTAP-negative, these cells were regarded as MPM cells. Thereafter, right pleural effusion worsened in the patient. In addition to bilateral pleural effusion and right pleural thickening, left pleural thickening was also observed. Left pleural biopsy showed that calretinin-positive and D2-40-positive atypical cells were proliferated in the left parietal pleura. Since atypical cells were BAP1-negative but MTAP-positive, these cells were thought to be newly developed MPM cells in the left parietal pleura, but not invasion of right MPM into the left pleural cavity.

Conclusion: It has been difficult to differentiate cases where MPM developed unilaterally and spread to the contralateral pleural cavity from those where MPM developed bilaterally. However, like this case, it is possible to find multicentric MPM developed in bilateral pleural cavities by using IHC of BAP1 and MTAP well.

Keywords: bilateral malignant pleural mesothelioma, BRCA1-associated protein 1, methylthioadenosine phosphorylase, immunohistochemistry

P162: Characterization of Claudin15 as a New Diagnostic Marker for Malignant Pleural Mesotheliomas

Watanabe M1, Higashi T2, Mine H1, Takagi H1, Muto S1, Okabe N1, Matsumura Y1, Hasegawa T1, Shio Y1, Sugimoto K2, Chiba H2, Suzuki H1

1Department of Chest Surgery, Fukushima Medical University, Fukushima, Japan, 2Department of Basic Pathology, Fukushima Medical University, Fukushima, Japan

Poster Session, Virtual, May 7, 2021

Objectives: Malignant pleural mesotheliomas (MPMs) is a fatal disease mainly caused by past exposure to asbestos. MPMs show variety of histopathological patterns, which often makes it difficult to diagnose MPMs correctly. Although a combination of several markers is currently used, development of more reliable markers is awaited. Claudins are four-transmembrane proteins and form a protein family consisting 27 members in humans. Specific combination of claudins are differentially expressed in different organs and form tight junctions with different permeability. CLDN15 is expressed in normal pleura specifically, and expression of CLDN15 has been known to be increased at mRNA level in MPMs. In this study, we investigated whether CLDN15 serves as a diagnostic and therapeutic target for MPMs.

Methods: From 2003 to 2019, 42 cases were diagnosed as MPMs at our hospital and partner hospitals. We made a new rat anti-CLDN15 monoclonal antibody, and established a hybridoma clone suitable for IHC. We immunostained 42 tissues with newly established anti-CLDN15 antibody, and compared the staining intensity and occupation with those of Calretinin, a known marker for MPMs. We also immunostained poorly differentiated
lung adenocarcinomas, which are sometimes hardly distinguishable with MPMs. We used the immunoreactive score (IRS) method to semi-quantify CLDN15 protein expression in the plasma membrane and cytoplasm and Calretinin protein expression in the nucleus. Each protein’s staining intensity is classified into four groups: 0 (negative), 1 (weak), 2 (moderate), and 3 (strong). Percentage of positive staining area in tumor cells is classified into five groups: 0 (<1%), 1 (1-10%), 2 (11-30%), 3 (31-50%), 4 (50%<).

**Results:** Of the 42 cases, the epithelial type was 28 cases, the biphasic type was 9 cases, and the sarcomatoid type was 5 cases. In the epithelioid and biphasic types, the positive rate of immunostaining for CLDN15 was lower than that of Calretinin. When used in combination, the positive rate of both markers reaches almost 100%. In sarcomatoid type, the positive rates of CLDN15 and Calretinin were 40% and 20%, respectively. Although the sample size was small, CLDN15 exhibited better sensitivity than Calretinin. When the cut-off value of IRS was set to 4, the CLDN15-high group had a significantly better prognosis than the CLDN15-low group. The positive correlation of the expression level of CLDN15 and survival could be explained by the degree of differentiation. Highly differentiated MPMs may retain the CLDN15 expression and have better prognosis.

**Conclusion:** We found that CLDN15 and Calretinin in combination can be used as a diagnostic marker for MPMs. It is possible that CLDN15 could be used as a prognostic marker for MPMs.

**P163: Heterologous Differentiation in Malignant Pleural Mesothelioma: Institutional Series of 55 Cases**

**Zhang Y**1,2, Brambilla C2, Rice A2,3, Robertus J2,3, Thway K1,9, Molyneaux P3,5, Jordan S6, Lim E3,6, Lang-Lazdunski L7, Popat S3,8,9, Moffatt M1,3, Cookson W1,3, Nicholson A2,3

1National Centre for Mesothelioma Research, National Heart and Lung Institute, Imperial College London, London, United Kingdom, 2Department of Histopathology, Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom, 3National Heart and Lung Institute, Imperial College London, London, United Kingdom

**Objectives:** Malignant pleural mesothelioma (MPM) with heterologous differentiation is a morphologically distinct but rare entity with less than 60 cases reported to date. This study sought to present the clinicopathological characteristics of a large institutional series and answer some of the questions laid down by previous studies.

**Methods:** We retrospectively reviewed our institutional diagnostic archive and referral files over the past 28 years. The diagnostic criteria for the heterologous components were in line with WHO Classification of Tumours of Soft Tissue and Bone. Metaplastic changes, presence of osteoclast-like giant cells (OGCs) without malignant osteoid or bone formation, pseudoangiosarcomatous changes without vascular marker expression, rhabdoid change without myoid marker expression and so-called “leiomyoid differentiation” were excluded. No minimum cut-off threshold for the amount of heterologous component was employed. Survival analysis was performed using Kaplan-Meier method.

**Results:** 55 cases were identified, including 19 from the archive and 36 from referral service. Mean age was 71.5 years, with M:F ratio of 4:1. Information on asbestos exposure was available in 65.4% (36/55) of which 86.1% (31/36) were positive. Estimated incidence among diffuse MPM was 1.2%. Heterologous components were almost exclusively seen in non-epithelioid MPM (53/55, 96.3%). Osteosarcomatous differentiation was the most common (32/55, 58.2%) followed by osteochondrosarcomatous (8/55, 14.5%), chondrosarcomatous (8/55, 14.5%), rhabdomyosarcomatous (5/55, 9.1%) and angiosarcomatous (2/55, 3.6%). OGCs were seen in a minority of osteosarcomatous components (7/40, 17.5%). The median overall survival of non-epithelioid MPM with heterologous differentiation was not significantly different from those without (p=0.658). Some cases showed predominant heterologous elements.
Conclusion: Our study confirmed findings from earlier studies that osteosarcomatous and chondrosarcomatous components represent the most common lineages of divergent differentiation in MPM, with predominant heterologous elements being a particular diagnostic challenge. Based on available evidence its presence does not exert prognostic impact in non-epithelioid MPM.

Keywords: Mesothelioma, heterologous differentiation, osteosarcomatous, chondrosarcomatous, angiosarcomatous, rhabdomyosarcomatous
**P164: Clarifying Diagnosis and Surgical Selection in 155 Patients with Peritoneal Mesothelioma; Early Oncologic Outcomes from a Monthly Video-conferencing National Multidisciplinary Team Meeting**

Brandl A1, Westbrook S1, Nunn S1, Arbuthnot-Smith E1, Mulsow J2, Youssef H3, Carr N1, Tzivanakis A1, Dayal S1, Mohamed F1, Moran B1, Cecil T1

1Peritoneal Malignancy Institute, Basingstoke and North Hampshire Hospitals, Basingstoke, United Kingdom, 2National Centre for Peritoneal Malignancy, Mater Misericordiae University Hospital, Dublin, Ireland, 3Good Hope Hospital, Heart of England NHS Foundation Trust, Birmingham, United Kingdom

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Peritoneal mesothelioma (PM) is a rare, primary neoplasm of the peritoneum with increasing incidence worldwide. Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has shown promise as a treatment strategy. A National PM Multi-Disciplinary Team (National PM MDT) video-conference meeting was established in the United Kingdom and Ireland in March 2016.

The aim of the National PM MDT was to plan optimal treatment for these patients and record outcomes to provide evidence of the benefits of centralisation and the need for National Funding of a peritoneal mesothelioma service.

**Methods:** Between March 2016 and December 2018, 155 patients with PM, referred to peritoneal malignancy centres in Basingstoke, Good Hope Hospital Birmingham, The Christie Hospital Manchester and Mater Misericordiae in Dublin, were discussed at the National PM MDT via video-conference. Oncologic outcomes were completed by a request via 'Demographic Batch Service' to the 'NHS Spine, Personal Demographic Service' on the 1st July 2020.

**Results:** In total, 155 patients (79 female:76 male) with a mean age of 57±17 years were discussed. To date 22/155 have had CRS and HIPEC and the median PCI in the surgical group was 17. Two-year survival from time of review at the National PM MDT was 85% for patients treated with CRS and HIPEC compared with 61% for patients who did not undergo surgery. Complete cytoreduction was achieved in 19/22, Clavien-Dindo grade I/II complications occurred in 16/22 with no Grade III/IV morbidity or 30 day in hospital mortality. The median follow-up was 25.3 months.

**Conclusion:** This centralised National PM MDT was effective at selecting patients suitable for CRS and HIPEC and advises on the optimal treatment strategy for patients unlikely to benefit from surgery. Good outcomes are achieved in carefully selected patients through a national MDT process.

**Keywords:** peritoneal mesothelioma, National MDT

---

**P165: Outcomes of Cytoreductive Surgery in Malignancy Peritoneal Mesothelioma: A Case Series**

Ding Y1, Guerra G1, O’Byrne K1

1Princess Alexandra Hospital, Brisbane, Australia

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant peritoneal mesothelioma is a rare but aggressive disease of the peritoneum. Survival outcomes are historically poor, in part due to the advanced disease burden after delayed and challenging diagnoses, as well as the lack of trials comparing various treatment options and categorising selection criteria for treatment. This study evaluated the outcomes of patients with malignant peritoneal mesothelioma (MPM) who underwent cytoreductive surgery (CRS) at a single, local institution.
**Methods**: A single-institution (Princess Alexandra Hospital, Brisbane) peritonectomy data registry was established. Three patients with MPM were identified and their follow-up and outcomes presented. A literature review was also conducted.

**Results**: Between 2009 and 2019, three patients underwent cytoreductive surgery. Hyperthermic intraperitoneal chemotherapy was not used in any of these cases. All three cases had epithelioid mesothelioma.

**Conclusion**: Our institution utilized CRS coupled with chemotherapy to treat MPM. There is growing evidence demonstrating the improved outcomes of surgical modality, either alone or in combination with immunotherapy, systemic chemotherapy, or hyperthermic intraperitoneal chemotherapy, thus advocating aggressive treatment especially in selected patients.

**Keywords**: malignant peritoneal mesothelioma, cytoreductive surgery, adjuvant chemotherapy, hyperthermic intraperitoneal chemotherapy

**P166: Retrospective Analysis of Efficacy and Safety of Cisplatin Plus Pemetrexed for Treatment-naïve Malignant Peritoneal Mesothelioma**


1Hyogo College Of Medicine, Nishinomiya, Japan,
2Hyogo College of Medicine Sasayama Medical Center, Tambasasayama, Japan

**Poster Session, Virtual, May 7, 2021**

**Objectives**: Mesothelioma of peritoneal origin has wider variation in treatment outcomes than mesothelioma of pleural origin, likely because peritoneal mesothelioma comprises borderline malignant variants and aggressive malignant peritoneal mesothelioma (MPeM). This study retrospectively evaluates the efficacy of first-line systemic pemetrexed and cisplatin chemotherapy in MPeM.

**Methods**: Twenty-four patients with histologically proven MPeM were treated with cisplatin plus pemetrexed as a first-line systemic chemotherapy. The response was evaluated radiologically according to standard Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Twenty-two patients underwent 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT) at baseline, and 13 were eligible for metabolic assessment. Furthermore, metabolic response was evaluated by the disease type of MPeM.

**Results**: Complete responses and partial responses were achieved in 2 and 9 patients, respectively. Overall response rate and disease control rate were 45.8% and 91.7%, respectively. Median progression-free survival and median overall survival (mOS) were 11.0 months and 15.8 months, respectively. Wet-type MPeM had significantly longer survival (40.9 months median) than other clinical types with mOS of 40.9 months vs. 15.5 months (P = 0.045). The baseline maximum standardized uptake value in 22 patients was 8.93 (range, 2.5-16.77). Of the 13 patients with assessable metabolic response, 3 patients were classified as complete metabolic response, 6 patients as partial metabolic response, 2 patients as stable metabolic disease, and 2 patients as progressive metabolic disease.

**Conclusion**: Systemic cisplatin plus pemetrexed is active for MPeM. Disparity with the outcome of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HiPEC) needs to receive more emphasis, since peritoneal mesothelioma has a 5-year survival rate of 50%.

**Keywords**: malignant peritoneal mesothelioma, cisplatin, pemetrexed
P167: Achieving Equity in Treatment and Support for Peritoneal Mesothelioma: Establishing the UK National Peritoneal Mesothelioma Multi-disciplinary Team

Westbrook S1

1Hampshire Hospitals / Mesothelioma UK, Aldershot, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: Peritoneal Mesothelioma (PM) is a rare cancer which develops in the lining of the abdomen. There are approximately 130 patients diagnosed with PM in the United Kingdom (UK) per year. Patients present with vague non-specific symptoms such as abdominal distension and pain which makes it difficult to diagnose.

PM patients’ needs are that of all cancer patients – sharing the same questions and hopes. They are cared for within larger cancer specialities and perhaps for these patients they feel they are not being recognised as having a rare cancer. It is important that the patient has an understanding of their rare cancer - knowledge of symptoms, outcomes, treatment options and treatment side effects.

The Peritoneal Malignancy Institute (PMI) at Hampshire Hospitals NHS Foundation Trust in Basingstoke, UK, facilitates a PM National Multi-disciplinary Team (NMDT) meeting. The NMDT offers advice and recommends treatment pathways. The NMDT Clinical Nurse Specialist (CNS) based at PMI and funded by Mesothelioma UK (MUK), can improve support for the patient and their family/carer.

Method: This review examined newly diagnosed PM (all types) cases referred to the NMDT over a 26 month period. It explored which speciality the patients present to and where they are managed. The CNS initiated contact (where appropriate) with the referred patient, their family and/or health care professional (HCP). The CNS discussed disease symptoms, management of symptoms, available treatment options including current UK clinical trials as well as allowing the patient to ask questions. The contact involved signposting to other services such as community palliative care teams, benefits and welfare advisors, genomics, local asbestos support groups and the patients regional MUK specialist nurse.

Results: 131 cases of newly diagnosed PM were reviewed at NMDT (September 2018 – December 2020). 28% presented to obstetrics and gynaecology, 20% colorectal surgery, 13% gastroenterology. 19% were referred to the NMDT by oncology, 18% thoracic oncology, 12% colorectal surgery. 75% had ongoing care and treatment with thoracic oncology. The CNS had contact with patients and/or family/carers in 50% of cases and contact with HCP’s in 44% cases. Common themes were documented, such as, not having access to a local specialist nurse or if they did their knowledge of PM disease was minimal, prolonged time to diagnosis and delay in starting treatment.

Conclusion: PM cases reviewed at NMDT represents just 46% of UK new cases per year. The patients are being managed in a variety of oncological, medical and surgical specialities; however, the majority are receiving ongoing care and treatment with thoracic oncologists, who have experience with treating pleural mesothelioma. The CNS plays a key role throughout the patient’s journey in supporting the patient and signposting to services. This review shows the importance of referring PM cases to a national specialist MDT to achieve treatment and support equity for those with this rare cancer. Priority should be given to establish the service offered by PMI and MUK, thus allowing patients to be empowered and make informed decisions.

Al-Demery A, Gaafar R, Mourad I, Ghaly G, Salama A, El-Attar I, Mohammed A

1Department of Surgical Oncology, National Cancer Institute, Cairo University, Egypt, Cairo, Egypt,
2Department of Medical Oncology, National Cancer Institute, Cairo University, Egypt, Cairo, Egypt,
3Department of Biostatistics and Epidemiology, National Cancer Institute, Cairo University, Egypt, Cairo, Egypt

Poster Session, Virtual, May 7, 2021

Objectives: The predicted incidence of pleural mesothelioma in Egypt will reach its peak around 2040. Mesothelioma is a loco-regional disease. Cytoreductive surgery and intracavitary treatment may be associated with better impact on disease control and survival.

To describe our surgical experience for managing pleural mesothelioma in Egypt. We analyze and compare the peri-operative sequelae and complications of both treatment options (radical surgery followed by hyperthermic intrathoracic chemotherapy “HITHOC”, versus radical surgery alone). We evaluate survival outcomes during the study period.

Methods: A prospective study was conducted, from January 2016 to January 2019, on 40 patients of malignant pleural mesothelioma undergoing surgical resection by either extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D) at the National Cancer Institute, Cairo University, Egypt. Of these, 20 patients “study group (A)” underwent surgery followed by HITHOC, using two drugs (cisplatin and adriamycin), while the other 20 patients had surgical resection only “control group (B)”. Criteria of our patients, the operative details regarding type of surgical procedure (EPP or P/D), and intra-operative sequelae during HITHOC as technical, cardiovascular and respiratory complications were analyzed. Pathological TNM staging was described. Early and late postoperative complications were investigated. Patients were followed-up during the study period.

Results: Our study included 15 males and 5 females in each arm. Their median age (in years) was 48.2 (HITHOC arm) & 52 (Control arm). Mean length of hospital stay of patients undergoing HITHOC was 10.1 days, while that of control group was 11.4 days (p=0.096). There was no postoperative mortality recognized in both arms. Atrial fibrillation, that occurred in 6 patients (30%) receiving HITHOC, and in 5 patients (25%) in the control group, was the most commonly observed morbidity. 7 patients (35%) in the HITHOC group had experienced disease recurrence during the follow up period, in comparison to the control group, in which 10 patients (50%) had disease relapse (p=0.02). The 1-year Disease Free Survival (DFS) was 68.8% in the HITHOC group, and 44% in the control group (p=0.031).

Conclusion: Surgical cytoreduction with HITHOC seems to be an innovative approach for pleural mesothelioma. This multimodal treatment, using cisplatin and adriamycin, is well tolerated by our patients and associated with an acceptable morbidity rate. It shows beneficial effects on the interval to recurrence and proportion of disease relapse.

Keywords: extrapleural pneumonectomy, pleurectomy/decortication, hyperthermia, intrathoracic chemotherapy, pleural mesothelioma, adriamycin, cisplatin, cardiotoxicity
P169: Pleurectomy/Decortication for Malignant Pleural Mesothelioma: A Single-Centre Experience

Berzenji L1, Michaux D1, Yogeswaran S1, De Bondt C1, Lauwers P1, Raskin J1, Hendriks J1, Van Meerbeeck J1, Van Schil P1

1Antwerp University Hospital, Edegem, Belgium

Poster Session, Virtual, May 7, 2021

Objectives: Despite the progress made in recent years regarding multimodal therapies, the exact role of surgery for MPM remains a controversial topic. Data from the last few years has shown that P/D achieves similar oncological results and similar or better overall survival rates when compared with extrapleural pneumonectomy (EPP). Moreover, P/D is associated with decreased postoperative morbidity and mortality rates. The aim of this study is to investigate early and long-term results in patients undergoing pleurectomy/decortication (P/D) for malignant pleural mesothelioma (MPM) in a single centre.

Methods: Clinical and pathological characteristics of MPM patients treated by P/D between January 2008 and December 2020 were retrospectively reviewed. Overall 30- and 90-day mortality and 1- and 2-year survival rates were calculated. Postoperative complications and disease progression or recurrence were analysed by descriptive statistics. Univariate and analyses and multiple regression of factors related to long-term survival were also performed.

Results: A total of 46 patients (34 male and 12 female patients) with an overall mean age of 65.2±7.3 years, underwent P/D for MPM. An extended P/D with (partial) resection of the pericardium and/or diaphragm was performed in 36 patients. Postoperative length of stay at the intensive care unit (ICU) and hospital stay were 4.1±2.0 and 18.3±6.9 days, respectively. Most frequent postoperative complications were pneumonia (26.1%), prolonged air leak (21.8%), and haemothorax (4.3%). The 30- and 90-day mortality rates were 2.2% and 4.3%, respectively. Overall 1-, and 2-year survival rates were 70.0% and 50.0%, respectively. Median survival time was 18 months (range 1-73 months). Recurrent or progressive disease occurred in 32 patients (72.3%). Multiple regression analysis revealed that age>70y, symptoms at diagnosis, T-status, N-status, addition of (neo)adjuvant therapy, the occurrence of postoperative morbidities, and progressive disease are significant prognostic factors (Table 1).

Conclusion: Patients treated with P/D for MPM have acceptable overall survival rates and an acceptable postoperative safety and complication profile. Careful preoperative evaluation and risk stratification is needed for patients that are eligible for P/D. Furthermore, multidisciplinary evaluation of all possible treatment options is necessary.

Keywords: Mesothelioma, Surgery, Pleurectomy/Decortication, Survival, Mortality, Morbidity, Complications
ABSTRACTS


Bölükbas S1, Baldes N1

1Evang. Kliniken Essen-Mitte, Essen, Germany, Essen, Germany

Poster Session, Virtual, May 7, 2021

Introduction: Whenever tumor infiltration of the lung parenchyma is present, anatomical or atypical resections are often required to achieve macroscopic complete resection (MCR) for the surgical treatment of malignant pleural mesothelioma (MPM). In the current work, the single-surgeon experience with the application of diode-dumped laser for surgical treatment of MPM is reported.

Methods: Between 12/2014 and 12/2020, all patients with MPM undergoing surgical therapy, where a diode-pumped laser for lung-sparing resection was utilized, were included in the current analysis. Data was collected prospectively and analyzed in a retrospective fashion.

Results: A total of 18 patients (four female) with a mean age of 66 (40–84) years were included in the analysis. All patients underwent standardized extended pleurectomy/decortication with systematic radical lymph node dissection. In all patients, tumor infiltration of the basilar lower lobe was present. Here, a diode-pumped neodymium-doped yttrium aluminium garnet laser was utilized for parenchyma-sparing lung resection. Macroscopic complete resection could be achieved in all patients. Heated-intraoperative chemotherapy was not performed in any patient. Laser-related morbidity or mortality did not occur. Despite the pre-surgical diagnosis, 5 out of 18 histologies were classified as non-epitheloid (4 biphasis, 1 sarcomatoid). The most common postoperative stages were IA in nine and stage IIIB in five patients, respectively. All patients underwent adjuvant chemotherapy with cisplatin/carboplatin and pemetrexed. Seven patients received immunotherapy in event of recurrence. Patients with epitheloid histology (n=13) had superior outcomes in terms median survival (35 [95%CI 23-47] vs. 10 months [95%CI 8-12], P=0.012), median progression-free survival (15 [95%CI 4-26] vs. 9 months [95%CI 3-15], P=0.067), respectively.

Conclusions: The above-mentioned surgical technique applying the diode-dumped laser represents a safe and effective method for parenchyma-sparing lung resection during surgery for MPM when lung infiltration is present. The outcomes are promising for patients with epitheloid histology. However, pre-surgical tissue diagnosis should be more reliable to avoid futile surgery in patients with non-epitheloid MPM.

Surgery; Mesothelioma; Laser

P171: Less-Invasive Approach for Macroscopic Complete Resection in Clinically Early Stage and Low-Volume Malignant Pleural Mesothelioma

Bölükbas S1

1Evang. Kliniken Essen-Mitte, Essen, Germany, Essen, Germany

Poster Session, Virtual, May 7, 2021

Background: Macroscopic complete resection (MCR) is the goal of surgery for the multimodal treatment of malignant pleural mesothelioma (MPM). Possibly due to systematic health surveillance for former asbestos exposed worker, more patients might be diagnosed with early stage and/or low-volume malignant pleural mesothelioma at our institution. Based on experience in minimally-invasive thoracic debulking surgery in selected ovarian cancer patients, we adopted this approach to clinically early stage and low-volume MPM patients. We report our first experience with less-invasive technique for MPM.

Methods: A video will demonstrate the surgical technique. We use one incision of 12 cm. No rib is excised. No rib spreader is used. One to two additional 1-cm ports for the camera and instruments are placed whenever needed. Pleurectomy/Decortication is performed by using a combination of conventional and endoscopic instruments and techniques following the standardized surgical protocol at our institution. Extensive visceral pleurectomy can be avoided using the diode-pumped Nd:YAG Laser LIMAX® 120 (wavelength: 1318 nm, Gebrüder Martin GmbH & Co KG, Tuttlingen, Germany) at a power output of 80 -100 watts for tumor destruction of small spots on
the visceral pleura. Partial resection of the diaphragm and pericardium as well as reconstruction is carried out whenever needed.

**Conclusion:** The goal of MCR might be accomplished less-invasively in clinically early stage and low-volume MPM. Less-invasive surgery offers MPM patients the generally known benefits as less morbidity, faster recovery and performance status preservation, respectively.

Surgery; Mesothelioma; less-invasive

---


**Culligan M**1, Ho S1, Marchese V1, Goloubeva O1, Friedberg J1

1University of Maryland School of Medicine, Baltimore, United States

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Lung-sparing surgery for malignant pleural mesothelioma (MPM) is associated with a difficult and prolonged recovery due to the extensive nature of the procedure. For a select group of patients, prolonged survival rates have been reported. A clear understanding of which patients will benefit from lung-sparing surgery is currently unknown. Despite having favorable tumor histologies, limited tumor burden and being deemed physically fit for surgery, some patients will still experience increased morbidity and/or mortality. These unfavorable outcomes will either delay or prevent a patient from receiving adjuvant treatments which ultimately negatively impacts their overall survival. By gaining a better understanding of the impact lung-sparing surgery has on a patient’s functional capabilities and health-related quality of life, surgical teams will be better able to identify appropriate surgical candidates, prepare them for surgery, support them through their recovery and ultimately improve their survival, quality of life and lived experience.

**Methods:** A retrospective review of 54 patients with MPM from 2015-2020 was performed. Physical functional performance in this cohort was measured using the Eastern Cooperative Oncology Performance Status Scale (ECOG). Post-operative patient outcomes were measured by tumor volume, chest tube days, ventilator days, hospital length of stay, percent of diaphragm preserved and phrenic nerve preservation.
Results: Statistical analysis identified that preoperative ECOG status was a significant predictor of patient outcomes. Prolonged hospital length of stay (> 14 days) and more days on the ventilator (> 59 days) were seen for those with ECOG = 1 vs. those with ECOG = 0, p-values are 0.02 and 0.03, respectively. The higher percentage of diaphragm preservation showed a trend toward to shorter hospital length of stay (p = 0.10), days on the ventilator (p = 0.08) and the number of chest tube days (p = 0.09). Neither tumor size nor phrenic nerve preservation impacted patient outcomes.

Conclusions: Analysis of the data generated from this study will serve as the foundation for continued research aimed at improving patient selection, decreasing symptom burden, improving functional capabilities and optimizing both health-related quality of life and patient experience. Knowing who will benefit from surgery and who will not benefit from surgery is a critical and currently unanswered question that multidisciplinary thoracic oncology teams ask every day. Our hope is that the results of this research will one day help teams to answer this question using scientific evidence to guide and support their decisions and recommendations.

P173: Factors Influencing the Prognosis of Malignant Pleural Mesothelioma: A 5-year Analysis from a Tertiary Referral Centre

Dawson A1,2, Kutywayo K1, Fennell D1,2, Nakas A1

1University Hospitals of Leicester, Leicester, United Kingdom, 2University of Leicester, Leicester, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: Extended pleurectomy decortication (EPD) for malignant pleural mesothelioma (MPM) is one modality of treatment offered to patients in order to achieve the greatest survival possible in this incurable disease. Whilst adverse prognostic factors have been identified, some widely accepted and others debated, we wished to assess the most important prognostic factors affecting overall survival in a tertiary referral centre from the United Kingdom.

Methods: An EPD database was retrospectively reviewed between August 2013 and July 2018. All patients undergoing EPD for MPM were included. Patients who died within 90 days from the date of surgery were excluded as were patients with a histopathologically confirmed sarcomatoid subtype of MPM. Demographic data along with neoadjuvant chemotherapy and haematological sampling data were collected. Survival times were calculated from the date of the operation until the date of death or last follow-up. Descriptive statistics were used to analyse the demographic and pre-operative data. Categorical data was analysed using Pearson Chi-Square, otherwise the Fisher’s exact test was used. Continuous data was analysed using the Mann-Whitney U test. Univariate analyses were performed using the Kaplan-Meier method with the log rank test. Multivariate analysis was performed using a forward stepwise Cox regression model. All statistical analysis was performed using the IBM SPSS Version 25.

Results: Over a five-year period, 187 patients with a diagnosis of MPM underwent EPD (152 (81%) male, with a median age of 68 years (IQR: 64-72 years)). The most common histopathological subtype was epithelioid in 164 patients (88%) and 55 patients had received neoadjuvant chemotherapy. The median follow-up time of this cohort was 16.6 months (IQR: 9.1-27.3 months). The median overall survival of the cohort was 16.9 months (SE: 1.6; 95%CI: 15.8-20.7 months). On univariate analysis: age at operation (>68 years) (p=0.013), biphasic histology (p=0.003), advanced stage (T3 or T4 disease) (p=0.017), low pre-operative haemoglobin (p=0.024), high neutrophil lymphocyte ratio (p=0.018) and high platelet lymphocyte ratio (p=0.026) were associated with a decreased overall survival. On multivariate analysis: age (HR: 1.59; p=0.07); biphasic histology (HR: 1.82; p=0.012), advanced stage (HR: 1.79; p=0.005), low haemoglobin (HR: 1.48; p=0.021) and neutrophil lymphocyte ratio (HR: 1.76; p=0.016) were retained in the multivariate model as an indicator of a poorer overall survival.

Conclusion: The results of this work echo the importance of preoperative histopathological diagnosis. The administration of neoadjuvant chemotherapy had no effect on overall survival nor did lymph node status (N0 vs N1/N2 or N0/N1 vs N2). This data provides evidence to support the haematological parameters of low haemoglobin, high neutrophil lymphocyte ratio and high platelet lymphocyte ratio as negative predictive factors for overall survival. This
data may be used to inform future trials involving surgery for MPM.

Keywords: Malignant pleural mesothelioma, Surgery, Extended pleurectomy decortication, Prognosis, Survival

**P174: The NCI-IASLC-MARF Joint Task Force System Captures Data That Has Potential to Standardize and Optimize Surgery-based Treatments for Malignant Pleural Mesothelioma**

**Friedberg J**¹, Culligan M¹, Khashab T¹, Naselsky W¹

¹University Of Maryland School Of Medicine, Baltimore, United States

**Poster Session, Virtual, May 7, 2021**

Objectives: Surgery, as part of a multimodal approach, appears to benefit some patients with malignant pleural mesothelioma. Comparing results and drawing conclusions about different treatments, however, is currently impossible due to extreme variability in: patient selection, surgical techniques, adjuvant treatments, and the cancer itself. This project aims to address that problem.

**Methods:** An NCI-IASLC-MARF joint task force recently published a proposed system for collecting data about patients undergoing surgery for malignant pleural mesothelioma. This system includes information about: the patient, the cancer, the details of the operation, and follow up/subsequent treatments. The system includes worksheets that capture detailed information about the operation, breaking the surgery down by different regions of the chest and capturing information about how the cancer was removed or treated in each region. The information from that worksheet is then used to generate a “completeness of resection” score. As a feasibility study, this worksheet and scoring system was tested on ten patients undergoing lung-sparing surgery for mesothelioma.

**Results:** At the conclusion of ten lung-sparing mesothelioma operations that lasted anywhere from 6–14 hours, the surgical details sheet was completed and the score for completeness of resection was then calculated.

Even at the conclusion of these long operations it took less than 10 minutes to complete the forms for each patient, including generation of the “Completeness of Resection” score (figure 1).

**Conclusion:** The Joint Task Force forms were user-friendly and time-efficient. If mesothelioma surgeons adopt this system, it would create a database with potential to answer: optimal patient selection criteria, optimal surgical techniques, and it could provide a “common denominator” for evaluating the effectiveness of different adjuvant therapies. It is hoped this system will be adopted, internationally, by mesothelioma surgeons. Ultimately, this could allow creation of a database that could yield information answering many unknowns about surgery-based treatments for mesothelioma.

**Keywords:** Mesothelioma, surgery, standardization
P175: Complications Associated with Extended Pleurectomy-Decortication Combined with Intraoperative Intrathoracic Povidone-Iodine Lavage for Malignant Pleural Mesothelioma

Friedberg J1, Naselsky W1, Culligan M1, Khashab T1, Sachdeva A1, Pickering E1, Holden V1, Mohindra P1, Scilla K1, Rolfo C1

1University Of Maryland School Of Medicine, Baltimore, United States

Poster Session, Virtual, May 7, 2021

Objectives: Surgery-based treatments for mesothelioma are neither standardized or even accompanied by level 1 evidence to establish their efficacy. They are typically operations of colossal magnitude performed with curative intent, but of palliative expectation. It is critical, therefore, that the complications surrounding the multitude of surgery-based treatments that are being performed be carefully recorded and reported.

Methods: Patients with mesothelioma confined to one hemithorax were offered lung-sparing surgery after being deemed safe and oncologically appropriate candidates by a multidisciplinary mesothelioma team. 47 patients underwent lung-sparing surgery with attempted complete macroscopic resection, followed by three 5-minute dwells of 10% povidone iodine in sterile water heated to 42°C. Patient operative reports and medical records were reviewed for demographics, complications, therapeutic interventions, length of stay, and discharge status.

Results: During the time period from March 2015 to October 2019, a total of 47 patients (79% male, age 35-85, median 67 years) underwent lung-sparing surgery with intraoperative povidone-iodine lavage. Macroscopic complete resection was achieved in 46/47 (98%) and 30- and 90-day mortality were 1/47 (2%) and 3/47 (6%), respectively. Median length of stay was 16 days, with 83% discharged directly to home. Air leak greater than 7 days 21/47 (45%) and atrial fibrillation 9/47 (19%) were the most common complications. Four (9%) patients underwent placement of endobronchial valves as part of the treatment for their air leaks, with one patient suffering an intraoperative arrest and becoming the only 30-day mortality. The complete list of complications is in Table 1.

Conclusion: This combination of lung-sparing surgery and intraoperative hyperthermic povidone iodine lavage resulted in complications in 36/47 patients (77%), ranging from minor to death. Despite this high complication rate, the mortality was in keeping with the lower end of most reported surgical series and over 80% of the patients were discharged directly to home. The mortality related to endobronchial valve placement for persistent air leak speaks to the caution with which this intervention should be considered. Meticulous and candid reporting of complications related to surgery-based treatments for mesothelioma is imperative if the international community is ever going to be able to collect the data required to develop the much-needed standardized surgical approach.

Keywords: Mesothelioma, pleura, surgery, adjuvant, complications

Table 1: Complications Following Extended-Pleurectomy Decortication and Intraoperative Intrathoracic Povidone-Iodine Lavage (N=47)

<table>
<thead>
<tr>
<th>Complications</th>
<th>Patients (%)</th>
<th>21 (45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air Leak, Lasting &gt; 7 Days</td>
<td>1/47 (2%)</td>
<td></td>
</tr>
<tr>
<td>Allergic Reaction to Povidone-Iodine</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>9 (19)</td>
<td></td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Chylo Leak</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Deep Vein Thrombosis</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Hypotension, Lasting &gt; 48 hours</td>
<td>8 (17)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (11)</td>
<td></td>
</tr>
<tr>
<td>Empyema</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>No Apparent Complications</td>
<td>11 (23)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedural Interventions</th>
<th>Patients (%)</th>
<th>1 (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed Chest Closure</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Endobronchial Valve Placement</td>
<td>4 (9)</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Percutaneous Gastrostomy</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Percutaneous Pigtail Catheter</td>
<td>4 (9)</td>
<td></td>
</tr>
<tr>
<td>Tracheotomy</td>
<td>2 (4)</td>
<td></td>
</tr>
</tbody>
</table>
**P176: Posterior Intercostal Lymph Nodes Are Highly Significant and Should Be Harvested During Any Therapeutic Operation for Malignant Pleural Mesothelioma**

**Friedberg J1, Simone, II C2, Culligan M1, Putt M1, Barasky A3, Katz S3, Naselsky W1, Khashab T1, Cengel K3**

1University Of Maryland School Of Medicine, Baltimore, United States, 2New York Proton Center, New York, USA, 3University of Pennsylvania School of Medicine, Philadelphia, USA

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Rarely described posterior intercostal lymph nodes represent one of the lymphatic drainage sites for the pleural space. These nodes were harvested during surgery for malignant pleural mesothelioma and their significance was evaluated.

**Methods:** As part of the thoracic lymphadenectomy during lung-sparing surgery for mesothelioma, the posterior intercostal lymph nodes were harvested in 56 consecutive patients. These nodes were accessed by incising the endothoracic fascia, paraspinally for 2-4 interspaces above and below the thoracotomy incision. The impact of these nodes on both progression-free and overall survival was then analyzed by multiple statistical methods.

**Results:** Median progression-free and overall survival were 11.6/25.5 months, respectively. In 6/56 (11%) posterior intercostal lymph nodes were the only positive nodes and, overall, 48.2% had posterior intercostal lymph node metastases. Patients with N2 disease had significantly poorer prognosis if the posterior intercostal lymph nodes were involved: PFS (7.3 vs 14.9 months, p=0.002) and OS (14.4 vs 26.1 months, p = 0.028). In the multivariable models, after adjustment for nodal stage and other prognostic factors, intercostal nodes remained associated with a 2.5 fold elevated risk of progression (p<0.001) and a 2.3 fold elevated risk of death (p<0.001) (See Figure 1). There were no known complications attributable to harvesting these lymph nodes.

**Conclusion:** Metastatic cancer detected in these lymph nodes independently more than doubled the risk of progression and death. In 11% of the patients these were the only metastatic nodes. In this series, these lymph nodes proved highly prognostic. Validation of these results by other groups is needed, but based on these findings it is recommended that the lymphadenectomy during any surgery for mesothelioma should include these nodes. Further studies are ongoing within our group with a different population of patients.

**Keywords:** Mesothelioma, surgery, lymphadenectomy, staging, outcomes
**P177: Concordance in Lymph Node Pathology Obtained via Endobronchial Ultrasound Guided Transbronchial Needle Aspiration vs Surgical Resection in Patients with Malignant Pleural Mesothelioma**

Grier W1, Friedberg J1, Culligan M1, Sachdeva A1, Holden V1, Glass E1, Khashab T1, Rolfo C1, Scilla K1, Mohindra P1, Pickering E1

1University Of Maryland Medical Center, Baltimore, United States

Poster Session, Virtual, May 7, 2021

**Objectives:** When treating malignant pleural mesothelioma (MPM), a select group of patients are offered extended pleurectomy and decortication (EPD). Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) of lymph nodes (LN) has become the standard modality for mediastinal staging in lung cancer; however, it is not routinely utilized in patients with MPM who are being considered for surgical resection. We compared the pathologic and staging concordance obtained via EBUS-TBNA to that obtained at surgical resection.

**Methods:** An analysis of a historical prospective cohort of patients who underwent both EPD and EBUS-TBNA at the University of Maryland Medical Center between March 2015 and February 2019 was performed to evaluate the concordance of pathology and cancer staging between both modalities. Data evaluated included total number of lymph nodes biopsied by EBUS-TBNA, pathology reports of LN from EBUS-TBNA, and surgical LN pathology. The definition of positivity was defined a priori as identification of malignant cells. Correlation between pathology and staging was evaluated.

**Results:** Twenty-eight patients underwent both EBUS-TBNA and EPD. A total of 133 LNs were sampled by EBUS-TBNA. Ten samples were positive for mesothelioma; 3 samples, atypical; 2 samples, suspicious; and 6 samples, non-diagnostic. The remaining 112 LNs sampled were negative. Compared to surgical pathology, 55 LNs were matched with 40 (71%) LNs concordant and 16 (29%) LNs discordant. There were 77 LNs biopsied by EBUS-TBNA without surgical correlation. Of the discordant LN pathology, 2 LNs were positive on EBUS but negative on surgical pathology, and 12 LNs were positive from surgery while negative on EBUS pathology. Of the LNs with discordant pathology, station 7 was responsible for 10 of the 16 samples (63%). EBUS and surgical staging were concordant in 15 (54%) cases and discordant in 13 (46%) cases. Twelve patients were upstaged at the time of surgery with 1 patient downstaged. This was most commonly due to pathologic discrepancies of station 7.

**Conclusion:** In this cohort of patients who underwent EBUS-TBNA and EPD, a majority (71%) of accessible lymph nodes were concordant with that obtained at surgical resection. Conversely, the staging via EBUS-TBNA as compared to surgical pathology was discordant in nearly half the cases. While the utility of EBUS-TBNA in the pre-operative surgical evaluation of patients with MPM being considered for EPD remains unclear, our data suggests that it is effective in ruling-out contralateral disease.

**Keywords:** EBUS-TBNA, biopsy concordance, lymph node

**P178: Surgical Outcomes and Risk Factors in Curative-intent Surgery for Malignant Pleural Mesothelioma from Japanese Nationwide Annual Database**

Hashimoto M1, Yamamoto H2, Hasegawa S1

1Department of Thoracic Surgery, Hyogo College of Medicine, Nishinomiya, Japan, 2Health Policy and Management, School of Medicine, Keio University, Tokyo, Japan

Poster Session, Virtual, May 7, 2021

**Objectives:** Using data obtained from a Japanese nationwide annual database with web-based data entry, we clarified surgical outcomes and risk factors of curative-intent surgery for malignant pleural mesothelioma (MPM).

**Methods:** The characteristics and perioperative data from 622 patients who underwent curative-intent surgery for MPM between January 2014 and December 2017 were entered into the annual National Clinical Database of Japan data sets. We divided the data into two groups according to the type of surgery (extrapleural pneumonectomy; EPP and pleurectomy/decortication;
P/D). Then we investigated and compared the surgical outcomes and risk factors of each group.

**Results:** EPP was performed in 279 patients, P/D in 322. Patient’s characteristics of each group (EPP vs P/D) were as follows: median age: 65 vs 67 (p<0.001); male sex: 89.5% vs 86.0%; co-morbidity: 44.1% vs 49.6%. Perioperative outcomes were as follows: median operation time: 478 vs 478 minutes; blood loss: 1500 vs 1470 g; blood transfusion: 57.0% vs 46.9% (p=0.015). Morbidity rates were 45.2% vs 35.9% (p=0.02). Heart failure was significantly frequent in EPP group (7.5% vs 0.6%, p<0.001), and air leakage was significantly frequent in P/D group (0% vs 22.4%, p<0.001). Thirty-day mortality rates were 1.1% vs 1.2%, and operative mortality rates were 3.2% vs 3.2%, respectively. Regression analyses revealed high age (> 65) was a significant operative risk factor in EPP group (OR 3.56; 1.26-8.56).

**Conclusion:** In Japanese nationwide annual database, surgical mortality and morbidity were not higher than other previous reports. Both EPP and P/D might be feasible procedure as curative-intent surgery for mesothelioma.

**Keywords:** extrapleural pneumonectomy, pleurectomy/decortication, curative-intent surgery, database

### Postoperative morbidity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total (n=622)</th>
<th>EPP (n=279)</th>
<th>P/D (n=343)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air leakage</td>
<td>77 (12.4%)</td>
<td>0 (0.0%)</td>
<td>77 (22.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bronchopleural fistula</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>33 (5.3%)</td>
<td>20 (7.2%)</td>
<td>13 (3.8%)</td>
<td>0.072</td>
</tr>
<tr>
<td>Empyema</td>
<td>16 (2.6%)</td>
<td>6 (2.2%)</td>
<td>10 (2.9%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>15 (2.4%)</td>
<td>7 (2.5%)</td>
<td>8 (2.3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Interstitial pneumonia</td>
<td>3 (0.5%)</td>
<td>1 (0.4%)</td>
<td>2 (0.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>5 (0.8%)</td>
<td>4 (1.4%)</td>
<td>1 (0.3%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Heart failure</td>
<td>23 (3.7%)</td>
<td>23 (7.5%)</td>
<td>2 (0.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>2 (0.3%)</td>
<td>1 (0.4%)</td>
<td>1 (0.3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>4 (0.6%)</td>
<td>1 (0.4%)</td>
<td>3 (0.9%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Re-visit (within 24 hours)</td>
<td>7 (1.1%)</td>
<td>4 (1.4%)</td>
<td>3 (0.9%)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

### Surgical outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (n=622)</th>
<th>EPP (n=279)</th>
<th>P/D (n=343)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (min)</td>
<td>478 (360-604)</td>
<td>478 (390-584)</td>
<td>478 (281-619)</td>
<td>0.12</td>
</tr>
<tr>
<td>Blood loss (g)</td>
<td>1490 (860-2285)</td>
<td>1500 (1000-2071)</td>
<td>1470 (720-2463)</td>
<td>0.27</td>
</tr>
<tr>
<td>Transfusion during surgery</td>
<td>320 (51.4%)</td>
<td>159 (57.0%)</td>
<td>161 (46.9%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Intraoperative injury of neighborhood organ</td>
<td>22 (3.5%)</td>
<td>12 (4.3%)</td>
<td>10 (2.9%)</td>
<td>0.39</td>
</tr>
<tr>
<td>morbidity</td>
<td>249 (40.0%)</td>
<td>126 (45.2%)</td>
<td>123 (35.9%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>30-days mortality</td>
<td>7 (1.1%)</td>
<td>3 (1.1%)</td>
<td>4 (1.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Operative mortality</td>
<td>20 (3.2%)</td>
<td>9 (3.2%)</td>
<td>11 (3.2%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
**P179: Incidence and Oncological Impact of Tumor Infiltration at Biopsy Site**

Hashimoto M¹, Nakamichi T¹, Kobayashi A¹, Nakamura A¹, Kuroda A¹, Matsumoto S¹, Kondo N¹, Tsujimura T², Hasegawa S¹

¹Department of Thoracic Surgery, Hyogo College of Medicine, Nishinomiya, Japan, ²Department of Pathology, Hyogo College of Medicine, Nishinomiya, Japan

**Methods:** A retrospective analysis was conducted on consecutive patients who underwent curative-intent surgery following neoadjuvant chemotherapy in our institution from August 2009 to March 2019. Tumor infiltration at biopsy site was pathologically examined with hematoxylin-eosin stain and immunohistochemical stains. Oncological impact of tumor infiltration at biopsy site was investigated using Kaplan-Meier analyses and log-rank test.

**Results:** One hundred and sixty consecutive patients were enrolled in this study. Of 160 patients, 11 patients were excluded from analysis due to absence of pathological examination of biopsy site. Characteristics of the remaining 149 patients were as follow; median age 66, right side 77 (51.7%), male sex 119 (79.9%), extrapleural pneumonectomy was performed in 41 patients (27.5%), and pleurectomy/decortication in 108 patients (63.5%). Tumor infiltration at biopsy site was observed in 79 patients (53.0%). Overall survival was significantly shorter in patient with tumor infiltration of biopsy site (median survival time; 38.0 months vs 55.2 months, respectively, p<0.05).

**Conclusion:** In the present study, tumor infiltration at biopsy site was more frequently observed than previously reported. Tumor infiltration at biopsy site predicted poor survival after curative-intent surgery for MPM.

**Keywords:** malignant pleural mesothelioma, pleural biopsy, tumor infiltration

**P180: Non-incisional Extended Pleurectomy–decortication for Left Side Malignant Pleural Mesothelioma**

Hida Y¹, Kaga K¹, Kato T¹, Fujiwara A¹, Shiina N¹, Ujiie H¹, Sasaki A¹, Yamasaki H¹

¹Hokkaido University, Sapporo, Japan

**Methods:** The patient was placed right decubitus position. Under posterolateral thoracic incision, the 6th rib was removed. All the parietal pleura and the posterior half and the 3cm diameter of the pericardium were dissected. The pleural reflection at the hilum was dissected by scrubbing the lung parenchyma towards pulmonary vessels. It is important not to pull parenchyma from the vessels, which can cause hemorrhage. Once the edge of the pleural reflection...
was grasped with the surgeon’s fingers, lung decortication was performed easily by pushing out the lung parenchyma with gentle traction the visceral pleura. In this case, the entire left lungs were decorticated without any macroscopic residual tumor. The pericardium and the left diaphragm were reconstructed with prostheses. The lung surface was covered with polyglycolic sheets. No fibrin glue or staples were used.

Results: The operation time was 301 minutes, and the estimated blood loss was 1200ml. The patient recovered without any complication except for air leakage. It did not require any intervention, and the thoracic tube was removed on the 14th postoperative day.

Conclusion: NiPD may achieve less residual tumor, less operation time, less blood loss.

Keywords: malignant pleural mesothelioma, pleurectomy, decortication, surgery

P181: Experience of Lung-Sparing Pleurodectomy/Decortication with Intra-operation Adjuvant Therapy for Malignant Pleural Mesothelioma in a Single Center in Taiwan

Wu Y1, Chang H1, Hsieh Y1
1Taoyuan General Hospital, Taoyuan, Taiwan

Poster Session, Virtual, May 7, 2021

Objectives: Malignant pleural mesothelioma (MPM) is a rare disease in Taiwan so far. The survival of this disease is poor. Very few hospitals in Taiwan can provide surgical treatment for this disaster disease. The purpose of this study was to assess survival for patients with MPM in a single center in Taiwan, utilizing lung-sparing surgery with extended pleurectomy-decortication combined with intraoperative photodynamic therapy (PDT) or hyperthermic intrapleural chemotherapy (HIPEC) for a better local control.

Methods: From 2012 to 2018, 13 patients underwent lung-sparing surgery and PDT for MPM in Taoyuan General Hospital, Taiwan. All patients had a preoperative diagnosis of malignant mesothelioma. All patients received lung-sparing radical pleurectomy/decortication (P/D) surgery and intra-operation PDT (5) or HIPEC (8), and adjuvant chemotherapy and radiotherapy for the living patients.

Results: Macroscopic complete resection was attempted achieved in all 13 patients. Thirty-day mortality was 7.7% (1 case due to surgical bleeding complication) and 90-day mortality was 31 % (4 cases). For other 9 patients, the mean overall survival (OS) were 23.9 months. Subgroup analysis revealed 6 patients with epithelioid type (OS: 29.8 months), 3 patients with sarcomatoid/biphasic/pleomorphic type (OS:12 months), 3 patients with early stage (IB) epithelioid type are all still alive with a mean following time of 41.7 months.

Conclusion: This is the first report for a single center in Taiwan devoted in lung-sparing P/D with intra-operation adjuvant therapy for MPM. In selective cases of epithelioid type and in early stage, the patients may have a better survival chance. We provide a treatment choice except chemotherapy and radiotherapy for Taiwan’s MPM patients.

Keywords: Malignant pleural mesothelioma, Lung-sparing pleurodectomy/decortication, Photodynamic therapy, Hyperthermic intrapleural chemotherapy

P182: Pleurectomy Decortication in the Treatment of Malignant Pleural Mesothelioma: Encouraging Results and Prognostic Implications Based on Experience with 355 Consecutive Patients

Lapidot M1, Gill R2, Mazzola E3, Freyaldenhoven S1, Jaklitsch M1, Swanson S1, Sugarbaker D4, Bueno R1
1Brigham and Women’s Hospital, Harvard Medical School, Boston, United States, 2Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, United States, 3Dana Farber Cancer Institute, Boston, United States, 4Baylor College of Medicine, Houston, United States

Poster Session, Virtual, May 7, 2021

Objectives: Surgery in MPM has shifted over the past 2 decades from extra-pleural pneumonectomy (EPP) to pleurectomy decortication (PDC). We examined perioperative and long-term outcomes in patients in whom PDC was the intended treatment.
**Methods:** All patients from 2007-2015 who underwent PDC were included. Clinical, operative and outcome data were obtained. Kaplan-Meier estimators and log rank test were used to compare the overall survival, and logistic regression models were used to assess the rates of specific complications in relation to staging.

**Results:** During the study period, 355 patients underwent thoracotomy with intended PDC in a single institution. MCR was achieved in 304 (85.6%). Among these, there were 223 (73.4%) males, 206 (67.8%) right sided, median age was 69.184 (60.5%) were epithelioid, 103 (33.9%) biphasic and 17 (5.6%) sarcomatoid. Intraoperative heated chemo was delivered in 267 (87.8%) of these cases and 231 (76.2%) of the patients also received adjuvant 202 (66.4%) and/or neo-adjuvant 66 (21.7%) cisplatin based intravenous chemotherapy. The 30 and 90-day mortality were 3.0% (95% CI: 1.0%-4.9%) and 4.6% (95% CI: 2.2%-7.0%) respectively.

Most complications were of low severity. Air leak over 14 days in 141 (46.4%), DVT diagnosed by surveillance in 64 (21.1%), Atrial fibrillation in 42 (13.8%), chylothorax in 24 (7.9%), Empyema in 23 (7.6%), pneumonia in 21 (6.9%), Hemothorax in 12 (3.9%), vocal cord injury in 11 (3.6%), acute renal failure in 9 (3%) and pulmonary embolus in 8 (2.6%). Other complications occurred at lower rates. Tendency towards higher rate of complications was associated (p=0.082) with advanced pre-operative tumor volume stage (stage/complication rate: 1/66.1%, 2/72.3%, 3/78.1%, 4/86.1).

Five-year survival in the entire MCR group was 21.3% and median survival was 23.6 months. The median 5-year survivals were best for patients with T1 and epithelioid histology (69.8 months/54.1%). Preclinical staging with tumor volumes based on CT was associated with median/5-year survivals of 1: 33.4/27.5%; 2: 23.6/25.0%; 3: 16.5/8.8% and 4: 15.0/0%.

In a multivariate analysis factors that were found to be independently associated with longer patient overall survival included Epithelioid histology, T stage, low tumor volume staging by pre-operative CT, receipt of adjuvant chemotherapy, IOHC treatment, Female sex and Length of stay shorter than 14 days.
Conclusion: PDC is feasible with low mortality in experienced centers and is associated with high but manageable rates of post-operative complications. The five-year survival of patients undergoing PDC with MCR in multi-modality setting is approaching 25% and higher depending on preoperative staging with CT tumor volume, sex and histological subtype. These results compare favorably with those described for EPP presumably due to lung preservation.

Keywords: Malignant Pleural Mesothelioma (MPM), Pleurectomy Decortication (PDC), Macroscopic Complete Resection(MCR)

P183: Prospective Validation of Our Multimodality Prognostic Score for Treatment Allocation of Malignant Pleural Mesothelioma Patients

Lauk O1, Greb D1, Hebeisen M1, Matter A1, Opitz I1

1Department Of Thoracic Surgery, University Hospital Zuerich, Zuerich, Switzerland

Poster Session, Virtual, May 7, 2021

Objectives: Based on our recently developed multimodality prognostic score (MMPS) for improved treatment allocation for patients with malignant pleural mesothelioma (MPM), we prospectively validated the score.

Methods: Eligible patients diagnosed with MPM underwent induction chemotherapy followed by macroscopic complete resection either with extrapleural pneumonectomy (EPP) or (extended) pleurectomy/decortication ((E)PD) (group 1) or palliative respectively no
surgery (group 2). According to the MMPS assessed after chemotherapy, MMPS considers tumor volume (>500cm^3), histological subtype (non-epitheloid), C-reactive proteine (CRP; >0.5mg/l), and response to chemotherapy (RECIST criteria: progressive disease). Each of them count as 1 point in case of applicability. Median overall survival (OS) was estimated from Kaplan-Meier curves for patients with surgery and per MMPS.

**Results:** Of consecutive 119 MPM patients intended to be treated between August 2011 and 2019, group 1 consisted of 89 and group 2 of 30 patients. 77.3% were treated with cisplatin/pemetrexed. All patients had pathological IMIG stage (8th version) IA- IIIB. 30-day mortality was 0% in the surgery group and 14.3% in group 2. The calculated MMPS was mainly ≤ 2. Overall survival according to the MMPS is shown in the graph.

**Conclusion:** In agreement with our previous data, this prospective study with data from 2011 on, proofed the benefit of the MMPS for patient allocation to surgery. Additional analysis of blood markers as additional variables for further improvement of our score are ongoing.

malignant pleural mesothelioma, prognostic score, macroscopic complete resection, blood markers
P184: Analysis of Respiratory Function after P/D with Ventilation Scintigraphy

Nakamichi T1, Nakamura A1, Kuroda A1, Hashimoto M1, Matumoto S1, Kondo N1, Hasegawa S1

1Department Of Thoracic Surgery, Hyogo College Of Medicine, Nishinomiya, Japan

Poster Session, Virtual, May 7, 2021

Objectives: It is reported that P/D (Pleurectomy / Decortication) is less invasive than EPP (Extrapleural Pneumonectomy) because of lung sparing. However, in spite of ipsilateral lung expansion, respiratory function after P/D was worse than we predicted. We evaluate respiratory function after P/D with ventilation scintigraphy.

Methods: Ventilation scintigraphy was routinely carried out at perioperative period at our department. Among consecutive 126 patients who underwent P/D from April, 2013 to July, 2019, ventilation scintigraphy was carried out in 102 patients before and 3 months after P/D. We analyze FVC (forced vital capacity), FEV1.0 (forced expiratory volume in 1 second) and also virtually calculated ipsilateral and contralateral FVC with right / left ratio of ventilation scintigraphy.

Results: The preoperative FVC and FEV1.0 was approximately at the same level regardless of laterality. FVC decreased by 43% and FEV1.0 decreased by 29% postoperatively. Additionally, ipsilateral FVC decreased by 62% and contralateral FVC also decreased by 8%. Decrease of contralateral FVC can be explained by postoperative pain, reduction of thoracic mobility. The right side operation had higher rate in decrease of ipsilateral FVC.

Conclusion: Respiratory function after P/D was decreased more than we expected from lung expansion in CT scan. Not only ipsilateral FVC, but contralateral FVC was decreased. We report analysis of respiratory function after P/D in consideration of ventilation scintigraphy.

Keywords: P/D, Respiratory Function, Ventilation Scintigraphy

P185: Unusually Long Survival Rates for Epithelioid Mesothelioma Patients Observed with a Controversial Surgical Approach and Intraoperative Povidone-Iodine

Naselsky W1, Friedberg J1, Culligan M1, Khashab T1, Sachdeva A1, Pickering E1, Holden V1, Mohindra P1, Scilla K1, Rolfo C1

1University of Maryland School of Medicine, Baltimore, United States

Poster Session, Virtual, May 7, 2021

Objectives: Surgery for mesothelioma is performed with curative intent, but palliative expectation. It has yet to be supported as efficacious by level 1 evidence. Still, a highly selected subset of patients does appear to benefit from a surgery-based approach beyond what would be anticipated without surgery. This report details the results of a single institution study combining standard chemotherapy with lung-sparing surgery and intraoperative hyperthermic povidone-iodine lavage.
Methods: During the period from March 2015 to August 2020, 50 patients were deemed safe and oncologically appropriate candidates for a surgery-based multimodal treatment by a multidisciplinary mesothelioma team. All patients had attempted macroscopic complete resection with a lung-sparing approach with intraoperative hyperthermic (42°C) povidone-iodine in sterile water lavages (3, 5-minute dwells). Cautery in lieu of resection was selectively performed, primarily on the visceral pleura, and counted toward macroscopic complete resection.

Results: 50 patients (78% male, age 35-85, median 67 years) underwent lung-sparing surgery with intraoperative povidone-iodine heated lavage (hydrogen peroxide used in 1 patient due to povidone-iodine allergy). Macroscopic complete resection was achieved in 48/50 (96%). Subtypes included 37/50 (74%) epithelioid and 13/50 (26%) non-epithelioid. 30- and 90-day mortality rates were 1/50 (2%) and 3/50 (4%), respectively. Median disease-free survival and overall survival rates for the 13/50 non-epithelioid patients were 5.5, and 10.5 months, respectively. Median disease-free survival for the epithelioid subtype patients was 20.2 months and overall median survival for the epithelioid patients has not yet been met at a mean follow-up of 1.7 years (see Figure 1). The addition of cautery, in lieu of complete resection, did not affect survival rates in epithelial patients (15/37).

Conclusions: This surgery-based approach appeared to have little to no impact on non-epithelioid patients and would not be recommended. For epithelioid patients, however, it yielded an unusually long overall survival with a commonly reported disease-free survival. Those patients that received selective use of cautery on the visceral pleura showed no difference in survival compared to those with complete surgical pleurectomy, indicating the potential for unconventional use of cautery to spare the need for extensive visceral pleural dissection. The reason for these results is unclear, but suggestive of an immune-type mechanism, perhaps related to the intraoperative treatment, that has allowed patients to live for prolonged periods with indolent recurrences. Further studies are ongoing.

Mesothelioma, surgery, povidone-iodine, pleurectomy
**P186: The Results of Tri-modality Treatment with Extrapleural Pneumonectomy, Radiation, and Chemotherapy for Mediastinal Lymph Node Positive Malignant Pleural Mesothelioma**

**Okabe K**1, Inokawa H1, Hayashi M1, Okita R1, Kawamoto N1

1Yamaguchi Ube Medical Center, Ube, Japan

**Poster Session, Virtual, May 7, 2021**

**Objectives:** For operable malignant pleural mesothelioma (MPM), our first choice is extrapleural pneumonectomy (EPP) followed by hemi-thoracic radiation and chemotherapy. The treatment strategy for mediastinal lymph node positive MPM is controversial. The results of multimodal treatment with EPP for pathologically mediastinal lymph node positive epithelioid MPM are reported.

**Methods:** 58 consecutive EPP for MPM from June 2006 to January 2019 in our hospital were reviewed. We have instituted a trimodality therapy protocol consisting of EPP, adjuvant 45-50.4 Gy hemithoracic radiation, and adjuvant CDDP plus PEM chemotherapy. Postoperatively, 14 cases were diagnosed pathologically as mediastinal lymph node positive epithelioid MPM, and these fourteen cases were investigated. Overall survival from the treatment start was calculated using Kaplan-Meier method. The prognosis data were updated in February 2019. This was one institutional retrospective study.

**Results:** 14 epithelioid MPM patients with pathologically positive mediastinal lymph node postoperatively were analyzed (Table). Median age at EPP was 62 years old (46-74). Female was 2, and male was 12. Right side was 5, and left side was 9. Median EPP time was 7 hours 31 minutes (5 h 50 m-8 h 56 m). 30 day mortality was zero. IMIG pathological stage was IV in 1 and III in 13. Adjuvant 45-50.4 Gy radiation was completed for 13 patients (93%). Adjuvant chemotherapy was given for 12 patients (86%). One patient had both induction and adjuvant chemotherapy. The table shows the station of the pathologically metastatic lymph node of each patient. 7 patients had one station metastasis, and the other 7 patients had two station metastases. Postoperative median follow-up period was 7 years and 3 months. 3 year survival, 2 year survival, and median survival of the 14 patients were 27%, 50%, and 30 months.

**Conclusion:** This tri-modality treatment strategy with EPP, radiation, and chemotherapy for pathologically mediastinal lymph node positive epithelioid MPM is feasible, and the prognosis has been greatly improved.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Meta station</th>
<th>Patient</th>
<th>Meta station</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td># 6</td>
<td>8</td>
<td># 8</td>
</tr>
<tr>
<td>2</td>
<td># 3</td>
<td>9</td>
<td># 7, pericardial</td>
</tr>
<tr>
<td>3</td>
<td># 7, # 8</td>
<td>10</td>
<td># 7, # 9</td>
</tr>
<tr>
<td>4</td>
<td># 8</td>
<td>11</td>
<td># 5, # 6</td>
</tr>
<tr>
<td>5</td>
<td># 4, # 7</td>
<td>12</td>
<td># 5, # 7</td>
</tr>
<tr>
<td>6</td>
<td>parasternal</td>
<td>13</td>
<td># 5</td>
</tr>
<tr>
<td>7</td>
<td># 7</td>
<td>14</td>
<td># 6, # 7</td>
</tr>
</tbody>
</table>

**Keywords:** malignant pleural mesothelioma, extrapleural pneumonectomy, radiation, chemotherapy, lymph node metastasis

**P187: The Results of Trimodality Treatment with Extrapleural Pneumonectomy, Radiation, and Chemotherapy for Epithelioid Malignant Pleural Mesothelioma after 2011**

**Okabe K**1, Inokawa H1, Hayashi M1, Okita R1, Kawamoto N1, Taguchi K1, Aoe K1

1Yamaguchi Ube Medical Center, Ube, Japan

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Extrapleural pneumonectomy (EPP) or Pleurectomy/Decortication (P/D) is performed for operable malignant pleural mesothelioma (MPM). IMIG guidelines
(Rusch V, et al. JTCVS 2013) concluded that EPP or P/D should be selected on the basis of disease distribution, institutional experience, and surgeon preference and experience. Our first choice is EPP followed by radiation and chemotherapy. If EPP is inappropriate, P/D followed by chemotherapy is performed. Our results of trimodality treatment strategy including EPP to treat epithelioid MPM after 2011 are reported.

Methods: 29 consecutive EPP for epithelioid MPM from February 2011 to January 2019 in our hospital were reviewed. We have instituted a trimodality therapy protocol consisting of EPP, adjuvant 45-50.4 Gy hemithoracic radiation, and adjuvant CDDP plus PEM chemotherapy. 25 patients were treated with this protocol. However, 4 patients were given induction chemotherapy, and referred to us. They were scheduled to undergo EPP and adjuvant radiation. Overall survival from the treatment start was calculated using Kaplan-Meier method.

Results: Median age at EPP was 60 years old (39-70). Female was 8, and male was 21. Right side was 15, and left side was 14. Median EPP time was 7 hours 7 minutes (5 h 50 m-10 h 37 m). No blood transfusion during EPP was 11 cases (40%). 30 day mortality was zero. IMIG pathological stage was IV 2, III 17, II 6, and Ib 4. Adjuvant 45-50.4 Gy radiation was completed for 25 patients (86%). Chemotherapy was given in 25 patients (86%). 23 of 29 patients (79%) completed trimodality therapy. Postoperative median follow-up period was 4 years and 2 months. 5 year survival, 2 year survival, and median survival of all 29 patients were 43%, 72%, and 59 months. Although many advanced cases were treated, median survival was almost 5 years. The following (1) – (7) were suspected reasons of significantly improved results. (1) Improvement of EPP procedures and postoperative managements (2) EPP for good condition cases, and P/D for poor risk cases (3) Higher rate of the intact peritoneum during the diaphragm resection (4) Frequent irrigation of the chest cavity from the beginning (5) Use of new surgical instruments and sheets after the specimen was taken out from the chest cavity (6) Aggressive correction of postoperative mediastinal shift (7) Increase of radiation: 45 Gy to 50.4 Gy

Conclusion: This trimodality treatment strategy with EPP, radiation, and chemotherapy for epithelioid MPM is feasible, and the prognosis has been greatly improved.

Keywords: malignant pleural mesothelioma, extrapleural pneumonectomy, radiotherapy, chemotherapy, epithelioid type

P188: Final Results of a Feasibility Trial Assessing Intrapleural Photodynamic Therapy Combined with Pleurectomy/Decortication Then Chemotherapy in Malignant Pleural Mesothelioma Patients

Scherpereel A 1,2,3, Munck C 1,2,3, Surmei E 1, Akkad R 1, Wasielewski E 1,2, Dusson C 1, Baert G 2, Deleporte P 2, Desbordes J 1, Porte H 1,2,3, Mordon S 2,3

1Hospital of the University (CHRU) of Lille, Lille, France, 2Inserm U1189 - ONCO-THAI - Image Assisted Laser Therapy for Oncology, Lille, France, 3University of Lille, Lille, France

Poster Session, Virtual, May 7, 2021

Objectives: Multimodal treatment associating surgery (pleurectomy/decortication, P/D) then IV adjuvant chemotherapy (platinum/pemetrexed) is an effective therapeutic option for some selected malignant pleural mesothelioma (MPM) patients. Intra-operative pleural photodynamic therapy (iPDT) has emerged as a promising option to improve this multimodal treatment outcome (Friedberg J, Ann Thorac Surg. 2017). The MesoPDT trial (NCT02662504) aimed at assessing the feasibility of such procedure outside the only two US expert centers performing multimodal treatment including iPDT to date.
Methods: A single-center pilot clinical trial was designed to assess the feasibility of iPDT protocol in Lille University Hospital. A pool of maximum six patients was expected in order to apply the iPDT protocol, and to assess its applicability and safety outside US center expert.

Results: In 2016-2017, four consecutive assessable patients were included and treated per protocol, reaching the study achievement cut-off. iPDT specific procedures have been applied and managed in partnership with US experts. The safety profile was globally favorable, as validated by an external independent board. The main severe and most specific adverse event (observed in 2 patients out of 4) was acute lung injury occurring within 72 hours after iPDT, which may lead to reversible respiratory distress, manageable with adequate intensive care. The 4 patients achieved the full scheduled protocol.

Conclusion: The iPDT multimodal treatment for MPM was applicable and manageable in a European expert center, involving local skills and dedicated teams. Mean overall survival was promising (31.2 months), similar to previous US results. A large phase II randomized, multicentric US trial assessing a similar MPM multimodal strategy (P/D, chemotherapy) ±iPDT is still ongoing in the USA (NCT02153229; UPENN and Roswell center).

Keywords: malignant pleural mesothelioma, pleurectomy/decortication, chemotherapy, PDT, photofrin

P189: Outcome of 272 Consecutive Pleurectomies for Malignant Pleural Mesothelioma (MPM) 2005–2020: 5-Years Survival Rate 32% in R0-1 Resections

Sørensen J, Ryom P, Santoni-Rugiu E, Jakobsen J, Ravn J

1Dept Oncology, Danish National Mesothelioma Center/Rigshospitalet, Copenhagen, Denmark, 2Thoracic Surgery, Danish National Mesothelioma Center/Rigshospitalet, Copenhagen, Denmark, 3Dept Pathology, Danish National Mesothelioma Center/Rigshospitalet, Copenhagen, Denmark, 4Thoracic Surgery, Danish National Mesothelioma Center/Rigshospitalet, Copenhagen, Denmark, 5Thoracic Surgery, Danish National Mesothelioma Center/Rigshospitalet, Copenhagen, Denmark

Objective: Extrapleural Pneumonectomy (EPP) has been replaced by Pleurectomy as the standard surgical procedure in MPM. All screenings for MPM surgical candidates in Denmark are performed at a Multidisciplinary Tumor Board at the Danish National Mesothelioma Center at Rigshospitalet, Copenhagen, where also all Pleurectomies take place. Our experience from the last 15 years is presented, with respect to both complications and survival rates.

Methods: MPM candidates for Pleurectomy had epithelioid or biphasic histology with < 50% sarcomatoid component, performance status (PS) 0 or 1, age ≤80 years, T1-3N0-1M0 on PET/CT imaging, no major comorbidities and sufficient pulmonary function test. All underwent preoperative mediastinoscopy or EBUS to exclude mediastinal nodal disease. Surgery was performed as a lateral thoracotomy with removal of parietal and visceral pleura and extended radical pleurectomy, if possible. All patients received 3 courses of neoadjuvant Platinum and Pemetrexed chemotherapy and, if organ function, toxicity, and PS allowed it, also 3 courses of the same adjuvant treatment.

Results: A total of 272 patients had Pleurectomy during 2005-2020, with a median of 15 Pleurectomies for MPM annually (range 7-30). All have been followed until January 22, 2021, or death. 82% were males, median age is 66.5 years, and 33.5% are alive. All Pleurectomies were performed by one out of only three surgeons who alternated for this type of surgery in MPM, together with the same surgical team during the years. Explorative surgery only was performed in 30 patients (11.0%) due to large tumor burden or severe fibrosis, while 56 (20.6%) had macroscopically incomplete R2 resection, and 186 (68.4%) had complete R0 or R1 extended Pleurectomy. A total of 55 patients (20.5%) had one or more in-hospital postoperative problems: Prolonged (>7 days) air leak (11.7%), re-operation due to bleedings/hematomas/diaphragmatic rupture (4.0%), atrial fibrillation (3.9%), pneumonia (1.8%), obstipation (1.4%), recurrens paraes (1.1%), and chylos (1.1%). The 30-days mortality rate was 0/272 (0%), and the 90-days mortality 2/272 (0.7%). Median survival rates for patients having R2 and R0-1 Pleurectomy were 32.7 months (95% confidence limits...
Conclusion: Pleurectomy for MPM is a safe procedure when performed in a high-volume hospital by high-volume surgeons, with 0% 30-days postoperative mortality and 0.7% 90-days mortality among 272 patients. The 32% 5-year and 20% 10-year survival rates in MPM patients having R0 or R1 resection is promising in this generally poor prognosis disease. However, further improvement is definitely necessary, and exploration of more efficacious neoadjuvant and adjuvant treatments, refinement of the surgery, and clarification of the role of radiotherapy in this setting are warranted.

P190: Mesothelioma Patients’ Experiences of Follow-up Care Across Three National Health Service Trusts in the United Kingdom

Davey Z1, Davey Z1

1Oxford Brookes University, Oxford, United Kingdom

Poster Session, Virtual, May 7, 2021

Objectives: The study aimed to explore mesothelioma patients’ experiences of care in three National Health Service trusts in the United Kingdom with different models of follow-up care: Oxford University Hospitals, Royal Berkshire and Buckinghamshire Healthcare National Health Service Foundation Trusts. By comparing three different hospital trusts we hoped to identify any commonalities and differences in follow-up approaches between them.

Methods: This study consisted of three phases: 1) documentary analysis to collate key service documents relating to mesothelioma patients’ follow-up pathways at the three trusts 2) interviews with mesothelioma patients to explore from their perspectives what they liked about their care pathways and what they felt could be improved 3) three consultation and priority setting meetings with key stakeholders, including patients, carers, specialist nurses and commissioners.

Results: Four key themes emerged from the interview data: 'efficiency versus time', 'building relationships', 'information' and 'linking services'. The interview data were presented at each of the consultation meetings where stakeholders identified the findings they felt were priorities for improving mesothelioma patient care.

Conclusion: Study findings will be used to produce recommendations that have been agreed by patients, carers, healthcare professionals and commissioners. These can promote the use of consistently high standards of care for all mesothelioma patients in the United Kingdom, by advocating for, and making suggestions for improving, best practice to enhance the patient experience of the care pathway.

Keywords: Mesothelioma patients, follow up, care pathways, qualitative, symptom management
**P191: Developing a Treatment Decision Support Tool for Managing Malignant Pleural Effusion in Patients Diagnosed with Mesothelioma**

Fatima A

1Shaukat Khanum Cancer Hospital, Lahore, Pakistan

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant pleural effusion (MPE) is a common, serious complication often seen in metastatic lung cancer and metastatic pleural mesothelioma. Currently no specific treatment option is available in order to treat metastatic pleural effusion seen in patients diagnosed with mesothelioma. Aspiration, thoracoscopy with pleurodesis, bedside pleurodesis and indwelling pleural catheter are various options. However, deciding among these options sometimes become very challenging for both patient and caregiver. Our study aims to develop a support tool in order to help caregivers and patients which may help in decision making for the treatment of MPE.

**Methods:** The study was carried out in Shaukat Khanum Memorial Cancer Hospital. 50 Patients with confirmed diagnosis of mesothelioma were included in the study. Informed consent was obtained and patients were interviewed. The design team worked with participants to develop outputs including patient timelines and personas.

**Results:** Management of Malignant pleural effusion was the first priority of the patients. Preferred treatment option chosen by patient was therapeutic thoracocentesis and IPC. Patients were more inclined towards receiving graphical and visual information rather than audio. The main influences on people’s decisions about their MPE treatment were personal aspects of their lives (e.g. how active they are, degree and intensity of complications after procedure, post procedure care and support). The design study developed a first prototype (i.e. a video representing a web-based support tool) to help people identify personal priorities and guide shared treatment decisions.

**Conclusion:** Future studies are needed to help identify criteria to guide the choice of therapy in individual patients. MPE is a commonly encountered clinical problem where Quality of life and palliation are the paramount goal in its management. Patient should be incorporated in the decision making process on clinical management.

**Keywords:** mesothelioma, Malignant pleural effusion

---

**P192: Management of Persistent Air Leaks Post Extended Pleurectomy and Decortication**

Grier W

1University Of Maryland Medical Center, Baltimore, United States

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Persistent air leak (PAL) can occur in patients who have undergone extended pleurectomy and decortication (EPD) for malignant pleural mesothelioma (MPM). It is associated with prolonged hospitalization and increased risk for infection; however, there is high variability in management of this complication. Additionally, the treatment of PALs specifically in this patient population is not well defined. Thus, we present a single-center experience of PAL management in patients with MPM post EPD.

**Methods:** An analysis of a historical prospective cohort of patients who underwent EPD at the University of Maryland Medical Center between March 2015 and February 2019 was performed. All patients who developed a PAL were included in study analysis. Data on patient demographics, pathologic diagnoses, and date of surgery were collected. A descriptive analysis of treatment modalities and complications of PALs was completed. Continuous variables were summarized as either means or medians; categorical variables, as proportions.

**Results:** Forty-three patients underwent EPD for MPM, and 15 developed post-operative PAL (35%). All these patients were men with a mean age 67.4 ± 6.9 years. All patients had epithelioid MPM, except for 2 patients who had biphasic tumor. Five (33%) of the PAL group had concomitant empyema. Six patients (40%) underwent treatment with blood patch pleurodesis only; 4 patients (27%), intrabronchial valve (IBV) placement only; and 4 patients (27%), both modalities. One patient had a metallic airway stent placed in the bronchus intermedius for a broncho-pleural fistula. Single blood patch pleurodesis successfully resulted in resolution of PAL in 50% (5/10), allowing for chest tube removal in a median of 3 days afterwards. When the blood patch pleurodesis failed or there were contraindications to performing it, then IBVs were placed. The 8 patients who underwent IBV placement
had them placed in the upper lobe with a median of 2 IBVs (range 1-3) for a median duration of 63.5 days (range 35-249). Chest tubes were removed in a median of 15.5 days (range 3-64) from IBV placement. Four patients (27%) died within 1-year of their EPD surgery.

Conclusion: PALs can occur in a significant number of patients post-EPD and appear to originate from the upper lobes. Blood patch pleurodesis is only moderately successful in management of post-EPD PALs. IBVs can be an efficacious option for patients with PAL who have failed blood patch pleurodesis or have contraindications to it. Further research evaluating post-surgical PAL management is needed for patients with MPM post EPD.

Objectives: Post-operative empyema can be difficult to treat and portends a high mortality rate. The management of empyema in patients with malignant pleural mesothelioma (MPM) who have undergone extended pleurectomy and decortication (EPD) has not been delineated. Early recognition, aggressive treatment and multidisciplinary management is imperative. We present a single-center experience of empyema management in patients with MPM post EPD.

Methods: An analysis of a historical prospective cohort of patients who underwent EPD at the University of Maryland Medical Center between March 2015 and February 2019 was performed. All patients who developed a post-EPD empyema were included in study analysis. Data on patient demographics, microbiologic diagnoses, date of surgery, and hospital length of stay were collected. A descriptive analysis of treatment modalities and complications associated with post-operative empyema was completed. Continuous variables were summarized as either means or medians; categorical variables, as proportions.

Results: Six patients (14%) developed post-operative empyema, despite the intra-operative administration of povidone-iodine solution. All patients were men with mean age 67.5 ± 6.7 years and epithelioid MPM, except for 1 patient who had biphasic tumor. Median time from surgery to the result of a positive culture was 65.5 days (range 23-108) with causative organisms listed in Table 1. All patients were treated with systemic antimicrobials. Five patients underwent betadine infusion and intrapleural antibiotic administration; 5 patients, intrabronchial valve (IBV) placement for concomitant persistent air leak; 4 patients, intrapleural TPA/DNase administration; and 1 patient, placement of a metallic airway stent in the bronchus intermedius for a broncho-pleural fistula. Intrapleural antimicrobials consisted of gentamycin in 4 patients, vancomycin in 3 patients, amphotericin B in 1 patient, and neomycin-polymyxin B in 1 patient. The median hospital length of stay was 28 days (range 16-211). One patient failed therapy and required creation of a Clagett window. One patient died within 1-year of his EPD surgery due to hypoxic respiratory failure.

Conclusion: Empyema can develop as a delayed postoperative complication and is frequently associated with persistent air leak. A multimodality approach is often used to optimize clearance of the infection, and a variety of intrapleural therapies are available. For patients with PAL, IBVs can facilitate use of intrapleural therapies to minimize
extravasation into the airways. The pathogenic organisms can be fungal, multi-drug resistant, or polymicrobial. Empyema management is challenging in this cohort; however, timely administration of antibiotics, pleural space drainage and airway occlusion to decrease PAL is important in its management.

Keywords: empyema, intrapleural antibiotics, intrabronchial valves

P194: Intrapleural Liposomal Curcumin as a Palliative Treatment in Malignant Pleural Effusion: A Phase I Study Protocol Establishing Safety and Feasibility

Hocking A, Farrall A, Newhouse S, Dougherty B, Scordillo P, Klebe S

1Department of Anatomical Pathology, Flinders University, Bedford Park, Australia, 2Department of Respiratory and Sleep Services, Flinders Medical Centre, Bedford Park, Australia, 3SignPath Pharma Inc, New York, United States

Poster Session, Virtual, May 7, 2021

Objectives: Curcumin, a polyphenol found in the spice turmeric, is cytotoxic towards mesothelioma cells in vitro and in vivo stimulating pathways of programmed cell death including apoptosis, autophagy and pyrotosis. Difficulties with clinical translation exist because of curcumin’s low solubility in aqueous solution and oils, instability at physiological pH, low bioavailability and rapid molecular transformation and degradation. We propose that curcumin could be instilled into the pleural cavity of patients with mesothelioma through tunnelled indwelling pleural catheters (TIPCs) to both reduce cancer burden and malignant pleural effusion accumulation. The purpose of this phase I study is to evaluate the safety, feasibility, tolerability and pharmacokinetic profile of a single dose of liposomal formulated curcumin (Lipocurc™, SignPath Pharma, Inc), administered via an existing TIPC in individuals with malignant pleural effusion. Participant population: A minimum of 9 participants are required to meet the objectives of this study. The key inclusion criteria
are an existing diagnosis of malignant pleural effusion, recurrent symptomatic pleural effusion where insertion of TIPC is clinically indicated, Eastern Co-operative Group Performance Status 2 or better, and the ability to give informed consent.

**Methods:** The safety of three dose levels of liposomal curcumin (100 mg/m², 200 mg/m² and 300 mg/m²) will be tested using a standard ‘3+3’ dose-escalation model. The insertion of a TIPC will occur at least one week before the administration of the liposomal curcumin to allow for monitoring and treatment of any potential post-procedure infections. A week after the insertion of the TIPC, participants will attend the clinic as an outpatient for suture removal and vacuum bottle drainage. Participants will then be admitted as a hospital in-patient for the intrapleural liposomal curcumin administration. Before intrapleural administration of the liposomal curcumin, the TIPC will be drained to dryness via the TIPC vacuum drainage bottle system. Liposomal curcumin will be administered at room temperature through the TIPC via an adaptor port (PleurX™ catheter Access Kit), followed by two sequential 10 mL flushes of room temperature sterile 0.9% saline. Participants will be monitored for 48 hours as an in-patient to monitor for any possible adverse events. Baseline and post-procedural studies will be performed as outlined in Table 1. Pleural fluid, plasma and pleural fluid cells will be analysed for curcumin and curcumin metabolite concentration by ultra-performance liquid chromatography mass-spectrometry.

**Keywords:** Malignant pleural effusion, curcumin, intrapleural, malignant pleural mesothelioma
**P195: Examining the Role of Anamorelin in Mesothelioma (The ANTHEM Study): Rationale and Protocol**

_Hoon S_1,2, Fyfe K_1, Bowyer S_3, Hawkins F_4,5, Jeffery E_6, McIntyre C_1,7, Creaney J_8, Monterosso L_9,10, Nowak A_3,8, Brims F_1,2

1Sir Charles Gairdner Hospital, NEDLANDS, Australia, 2Curtin Medical School, Curtin University, Perth, Australia, 3Department of Medical Oncology, Sir Charles Gairdner Hospital, Nedlands, Australia, 4Department of Palliative Care, Sir Charles Gairdner Hospital, Nedlands, Australia, 5Faculty of Health and Medical Sciences, University of Western Australia, Nedlands, Australia, 6School of Public Health, Curtin University, Perth, Australia, 7Exercise Medicine Research Institute, Edith Cowan University, Perth, Australia, 8School of Medicine and Pharmacology, University of Western Australia, Nedlands, Australia, 9University of Notre Dame, Perth, Australia, 10St John of God Hospital Murdoch, Murdoch, Australia

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Cachexia is common in people with malignant mesothelioma (MM); about half of patients with MM have malnutrition and half have low skeletal muscle mass. Malnourished patients have worse quality of life (QoL), and cachexia may be associated with shorter survival in MM. A history of weight loss at the time of diagnosis is strongly associated with poor survival.

Ghrelin is a key regulator of appetite and weight. Ghrelin stimulates appetite and gastric emptying, leading to increased food intake, body weight, and appendicular skeletal muscle mass (ASM). Anamorelin is an orally administered ghrelin receptor agonist that improves body weight, ASM, appetite and QoL in people with advanced cancer. Anamorelin is well tolerated with no dose-limiting toxicities identified to date.

The aim of this study is to examine the efficacy of anamorelin in improving ASM and patient-reported outcomes in MM patients with cachexia, and to identify biomarkers associated with cancer cachexia in MM.

**Methods:** This is a single centre, phase II, randomised, placebo controlled cross-over study. Each 28 day treatment period is followed by a 3-day washout. Forty patients will be randomised to receive anamorelin in period 1 or period 2. The primary outcome is change in absolute ASM relative to height measured by Dual-Energy X-Ray Absorptiometry (DXA) scan at 28 days (end of period 1). Secondary outcomes include weight change, body mass index (BMI), cancer specific and cachexia-related QoL (FACT-L; Anorexia Cachexia Scale), objective physical activity (accelerometry), dietary intake, and patient preference for period. Tertiary outcomes are correlative biomarkers of cachexia and nutrition. Outcome measures will be collected at baseline, end of period 1 and at the end of period 2.

Eligible patients will have confirmed MM, ECOG 0-2, expected survival > 3 months and cachexia (defined as >5% unintentional weight loss in 6 months, or >2% in patients with BMI < 20). Patients will be excluded if they have peritoneal MM, significant cardiac co-morbidity, hepatic dysfunction, concurrent chemotherapy or radiotherapy (immunotherapy is accepted), concurrent use of appetite stimulants, uncontrolled diabetes mellitus, significant active gastrointestinal disease or inability to swallow oral tablets.

Recruitment will begin early 2020.

**Results:** Results of this trial will be reported in peer-reviewed publications and in conference presentations.

**Conclusion:** This study will provide vital pilot data to inform the role of anamorelin in MM patients with cachexia.

---

**P196: Impact of Symptoms and Physical Function on Quality of Life in Malignant Pleural Mesothelioma: Baseline Findings of an Ongoing Prospective Trial**

_Malec M_1, Barry T_1, Rose B_1, Wroblewski K_1, Mendoza A_1, Kindler H_1

1University Of Chicago, Chicago, United States

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Malignant pleural mesothelioma (MPM) is known to have high symptom burden and poor quality of
life. Given its poor prognosis, the importance of effective symptom management and minimizing impact on quality of life is paramount. The objective of this study is to better characterize the symptoms experienced by patients with MPM and the relationship between symptom burden, physical performance status and quality of life.

**Methods:** Consecutive patients were enrolled in a prospective, single-center, cohort study of MPM patients attending a mesothelioma clinic. Patient and mesothelioma characteristics were recorded at time of enrollment. Baseline symptom and quality of life assessments and performance status were assessed via the EORTC QLQ-C30 and LC13 measures. Physical performance was measured with the Short Physical Performance Battery (SPPB). The DN-4 questionnaire for neuropathic pain and the short form McGill Pain questionnaire were used to further characterize pain. The EAT-10 swallowing screening tool was used to further evaluate complaints of dysphagia.

**Results:** Fifty-six patients enrolled from June to October 2019. Baseline characteristics: median age was 68.5 (40-89); 36 (64.3%) were male and 100% were Caucasian. Tumor histology was epithelioid in 44 (78.6%), sarcomatoid 4 (7.1%), biphasic 5 (8.9%), and desmoplastic 3 (5.4%). A pleural effusion at diagnosis occurred in 44 (78.6%) of patients. Almost half (49.1%) had undergone surgery: 2 underwent extrapleural pneumonectomy; 24 had an extended pleurectomy/decortication. Chemotherapy was administered to 87.3%; immunotherapy to 41.2%; and 16.7% had undergone palliative radiation. The most commonly reported symptoms were fatigue in 46 (82.2%), which was moderate or severe in 15 (26.9%), followed by SOB, 41 (73.2%), mod/severe 9 (16.1%), pain in 31 (55.4%), mod/severe 9 (16.1%) and poor appetite 20 (35.7%), mod/severe 8 (14.3%). The average EORTC QOL/GLOBAL HEALTH score (possible range 0-100) was 69.6 (SD=18.8). The Spearman rank correlation coefficients between EORTC QOL/GLOBAL HEALTH score and SPPB were as follows: total score = 0.44, p<0.001, n=56, Chair stand score = 0.38, p=0.003, n=56, Gait score = 0.26, p=0.054, n=55, Balance score = 0.14, p=0.31, n=55. The Spearman rank correlation coefficients between EORTC QOL/GLOBAL HEALTH score and symptoms were as follows: SOB = -0.54, p<0.001, n=56, pain = -0.26, p=0.054, n=56, fatigue = -0.72, p<0.001, n=56, poor appetite = -0.50, p<0.001, n=56.

**Conclusion:** The most common symptoms experienced by MPM patients were fatigue, shortness of breath, pain and poor appetite. Of these, increased SOB, fatigue and anorexia were significantly associated with worse QOL. Higher SPPB total scores were associated with better QOL. This appeared to be primarily driven by the chair stands component. Longitudinal measurement will continue for up to one year. Better characterization of symptoms and the relationship between symptom burden, physical performance status and quality of life will be used to guide the types and timing of supportive interventions to be considered for further study by focusing on the factors most associated with declining quality of life.

**Keywords:** quality of life, symptoms burden, physical performance status

---

**P197: Mesothelioma and Cough: An Exploration of the Literature**

**Slaven K**

1Royal Papworth Hospital, Cambridge, United Kingdom,  
2Mesothelioma UK

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Mesothelioma is a devastating disease with a poor prognosis. Therefore, effective and timely symptom control is crucial. Patients may experience a variety of symptoms with pain and breathlessness being most associated with the disease. Cough can be an irritable and debilitating symptom experienced by 41% of patients with mesothelioma (Mesothelioma UK, 2020); although as a symptom, it is often dismissed. Cough is a problem that has physical, psychological and social consequences for the patient and their families and is responsible for significant morbidity. This literature search will inform a research proposal exploring the experience of cough in patients with mesothelioma.

**Methods:** A preliminary search through relevant literature has revealed a dearth of information about cough relating to mesothelioma and how to address it as a symptom. Key texts do not address cough. However, there is a significant amount of evidence concerning cough in the patient with lung cancer (Molassiotis et al, 2011; Yorke et al, 2015). Patients with lung cancer and those with mesothelioma may not have the same physiological mechanisms present and may therefore have different experiences of cough
requiring alternative approaches to symptom management. Mesothelioma patients with cough (4 people) attending a support group were asked an introductory series of questions to establish whether cough was identified as a subject in need of research.

**Results:** Patients reported that cough was a ‘debilitating symptom’ that caused ‘disruption to quality of life’. All felt it was a symptom that was ‘overlooked’ by healthcare professionals who tended to focus on breathlessness and pain as a priority. The patients reported that they felt ‘embarrassed by coughing’, ‘exhausted’ and ‘scared’. Its ‘unpredictable’ nature caused distress. They reported that their families felt ‘irritated’ by the cough. The group felt that it was an issue worthy of further exploration.

**Conclusion:** The author will apply for a small grant to explore this further including commonalities and differences between cough in lung cancer and mesothelioma. The hope is that this study will help the understanding of the experience of cough in mesothelioma and inform the management of cough by the individual patient, their carers and health care professionals.

**References:**


Cough, Mesothelioma, Experience

**P198: A Randomised Open-label Phase I/II Study Adding ONCOS-102 to Pemetrexed/Cisplatin in Patients with Unresectable Malignant Pleural Mesothelioma – 21 Month Analysis**

Aix S, Medical Oncology, Hospital 12 Octubre, Madrid, Spain, Cedres S, Isambert N, Medical Oncology, Centre Hospitalier Universitaire de Poitiers, France, Jaderberg M, Research & Development, Targovax ASA, Norway, Kuryk L, Research & Development, Targovax ASA, Norway, Levitsky V, Research & Development, Targovax ASA, Norway, Moller A, Research & Development, Targovax ASA, Norway, Paz-Ares L, Ricordel C, Pulmonology, Centre Hospitalier Universitaire de Rennes, France, Serres X, Radiology, University Hospital Vall d’Hebron, Barcelona, Spain, Vetrhus S, Research & Development, Targovax ASA, Norway

**Poster Session, Virtual, May 7, 2021**

Malignant pleural mesothelioma (MPM) is a rare, aggressive malignancy without curative treatment. Majority of patients (pts) receive pemetrexed/cisplatin as standard of care (SoC). median overall survival in unresectable disease is 12 months. ONCOS-102 is a granulocyte-macrophage colony stimulating factor (GM-CSF) expressing oncolytic adenovirus (Ad5/3-D24-GMCSF) with a unique ability to both prime and boost immune responses.

**Objectives:** The aim of the study was to assess immune and clinical responses as well as safety in pts with 1st and 2nd line unresectable MPM. Primary objective was safety and tolerability. Secondary objectives were ORR, PFS, OS and immunological activations as well as correlation between immunological activation and clinical outcome. 6 pts received the experimental treatment in a single-arm safety lead in followed by a randomised phase with 14 experimental and 11 control pts.

**Methods:** Eligible pts (experimental arm, n=20) received ONCOS-102 given intratumorally under CT or US guidance at a dose of 3 x 1011 VP on Day 1, 4, 8, 36, 78 and 120 plus six cycles of SoC starting on Day 22. The control group (n=11) received only SoC. Imaging was done at baseline, Day 43-64 and 127-148. Pts were monitored regularly for immunological assessment including lesional biopsies (baseline and Day 36).

**Results:** There were no safety concerns nor DLTs. In 1st line patients ORR/DCR was 30%/90% in the experimental group and 33%/83% in the control group. 2nd line pts
had ORR/DCR of 11%/67% in the experimental group and 60%/80% in the control group. mPFS was 9.8 months in the experimental group and 7.6 months in the control group. 21month survival rate in 1st line pts was 50% in the experimental group and 17% in the control group. Final mOS are still to be reached although in 1st line experimental pts will be at least 20.2 months while maximum 13.5 months in control pts. Profound innate and adaptive immune activation was observed in the experimental vs control group that was associated with better clinical outcome. ONCOS-102 treatment resulted in increase of intra-tumoral cytotoxic T-cells, polarization from M2 to M1 macrophages and PD-L1 upregulation.

**Conclusion:** ONCOS-102 in combination with SoC chemotherapy was well tolerated. Preliminary survival data show extended survival in ONCOS-102 treated 1st line patients compared to SoC chemotherapy. Changes of immune cells in ONCOS-102 patients were associated with better clinical outcome. Activation of adaptive and cytotoxic immune cells, PD-L1 and M2 to M1 macrophage polarization indicate that ONCOS-102 is able to induce a favourable tumor micro environment modulation thus providing a scientific rationale for combination with check point inhibition.

Trial registration: ClinicalTrials.gov NCT02879669

Ethics Approval: This study was approved by the IRBs of all the participating sites in Madrid, Barcelona, Rennes and Poitiers.

**P199: What Are the Psychological Effects of Mesothelioma on Patients and Their Carers? A Scoping Review**

**Sherborne V**

**Poster Session, Virtual, May 7, 2021**

**Objectives:** Despite recent advances in medical research, malignant mesothelioma remains an incurable and devastating disease, typically bringing shock and emotional distress to patients and their carers. Very little research has addressed the psychological impact on either group. The purpose of this scoping review was to examine the current state of the field and to identify areas for further research.
P200: MAGS: The Healthcare Staff Mesothelioma Asbestos Guidance Study

Angela Tod

Poster Session, Virtual, May 7, 2021

Objectives: To develop a critical account of the experiences of presentation, diagnosis, treatment and care for healthcare staff with mesothelioma

Methods: i) Rapid review of the literature searching for academic and grey literature, and online resources; ii) Freedom of Information (FOI) Request seeking the number and demographic details of healthcare staff who had sued the NHS for negligent exposure to asbestos resulting in mesothelioma; iii) semi-structured interviews with healthcare staff diagnosed with mesothelioma or their partners.

Results: The literature review and the interviews gave data from doctors, nurses and care assistants. One interview related to a health service manager. No interviews or data related to other ancillary staff such as porters or laundry staff, although such staff do get mesothelioma. Amongst the themes that emerged were that healthcare staff a) were sometimes treated as colleagues rather than patients and b) felt irony or anger that they had developed the condition from working in healthcare. The FOI request indicates a level of mesothelioma in healthcare staff far higher than that shown by Office of National Statistics (ONS) mortality data even though a) the request only covered England and b) many healthcare staff do not make a legal claim against the NHS. From 2002-15 there were 177 deaths recorded in the NHS Professions in the ONS data for Great Britain; from 2004-17 there were 961 claims made against the NHS in England.

Conclusion: The ONS data misrepresents the situation regarding the dangers of asbestos for healthcare staff. Healthcare staff, particularly managers, need to be more aware of the dangers of asbestos at work. We make a number of recommendations, for example, relating to how care is delivered to healthcare staff as patients.