

Executive Summary

National Cancer Institute Thoracic Malignancy Steering Committee

**National Cancer Institute-International Association for the Study of Lung Cancer-Mesothelioma
Applied Research Foundation**

Mesothelioma Clinical Trials Planning Meeting

March 29-30, 2017

Meeting Co-Chairs: Anne Tsao, M.D. and Shakun Malik, M.D.

Meeting Description

The National Cancer Institute (NCI) Thoracic Malignancy Steering Committee (TMSC) convened a Clinical Trials Planning Meeting for Malignant Pleural Mesothelioma (MPM) on March 29-30, 2017 in Bethesda, Maryland. The meeting was co-sponsored by the NCI, the International Association for the Study of Lung Cancer (IASLC), and the Mesothelioma Applied Research Foundation (MARF). The purpose of the meeting was to develop a strategy for two to three clinical trials for MPM within the National Clinical Trials Network (NCTN) that are feasible, statistically robust, and clinically meaningful in this rare disease that lacks randomized trials. The meeting attendees included TMSC members, mesothelioma clinicians, biostatisticians, a patient advocate, and staff from the NCI and the U.S. Food and Drug Administration (FDA).

Background

MPM is a rare, asbestos-related cancer with an estimated 3,000 new cases diagnosed annually in the United States (1, 2). Although asbestos exposure in the United States has diminished in recent decades, a steady number of people still develop mesothelioma, as the latency period varies from 20 to 50 years after exposure. In developing nations with limited regulations, mesothelioma poses a substantial global burden. MPM causes its morbidity and mortality primarily by local invasion, with the majority of deaths occurring from cardiopulmonary compromise. Despite recent advances in the understanding of the etiologic mechanisms, the prognosis for most patients diagnosed with MPM remains dismal and new therapies are desperately needed (3, 4).

Most of the available clinical information about early-stage MPM treatment is derived from retrospective or small clinical studies and thus there is no consensus as to the optimal treatment (5-8). The largest prospective study of trimodality therapy [neoadjuvant chemotherapy, extrapleural pneumonectomy (EPP), and adjuvant radiation] reported a median overall survival of 17 months (5). However, the use of surgical resection remains under debate as in the United Kingdom, the MARs trial randomized patients to EPP versus best supportive care and reported no survival benefit with EPP (4). In the unresectable setting, the combination of pemetrexed and cisplatin is the only FDA-approved

regimen for patients (9). Recently, the French MAPs trial showed a 2-month median overall survival benefit with the addition of bevacizumab to cisplatin-pemetrexed; yet to date, bevacizumab has not received EMEA or FDA approval (10).

Consensus & Recommendations

The meeting was organized into several sessions, each of which consisted of several speaker presentations followed by a panel discussion. As a result of these discussions, the following recommendations for clinical trials in MPM within the NCTN and in collaboration with international partners were made. The recommendations also delineate the need for standardization in many aspects of clinical and research practice to facilitate the conduct and comparability of network trials and advance translational research in MPM.

Early Stage Disease

- Mesothelioma surgical trials should be conducted in limited institutions that have the ability to standardize surgical practice, collect data reliably, perform the required translational correlates, and provide adequate safety for patients in a tertiary care center.
- A stable platform for surgical technique is needed with standardized definitions of the required preoperative procedures, types of surgeries performed, what constitutes a “resectable” patient, identify the standard follow-up period and interval, and define the operative report components.
- Imaging techniques remain a major challenge since few radiologists are familiar with how to conduct RECIST and modified RECIST in mesothelioma. Volumetric computed tomography (CT) is a potential improved measurement system and education in the use of this method radiographic reporting will be required to expand its use, potentially via a webinar that could be developed by the IASLC.
- Trials evaluating the sequence of tri- and bi-modality therapy are still needed as well as radiotherapy trials, e.g. P/D ± intensity-modulated radiation therapy (IMRT).
- Reproducing a single center’s trial experience (e.g., preoperative radiation therapy and EPP and postoperative chemotherapy, or the use of postoperative IMRT after P/D) in a multi-center environment to standardize or validate a therapy is a reasonable trial proposal.

Metastatic Disease

- All trials should collect translational correlates before, during (ideally), and after disease progression.
- Translational correlates should include specimens from blood, pleural effusion, and tumor (primary and metastatic).

- The limited number of patient accruals represents a major obstacle to the successful conduct of studies and hence the need for more reasonable inclusion/exclusion criteria should be emphasized.
- Critical components for future trial design includes avoiding duplication of pharmaceutical industry studies and focusing on scientific questions instead of the drug regulatory pathway.

Biomarkers

- Pathology uniformity is needed to denote the necessary reported components, define a core panel of biomarkers that should be conducted, and standardize specimen collection techniques for blood/pleural effusion/tumor tissue.
- There is a critical need to obtain translational correlative specimens before, during and after progression on systemic therapy.
- Window-of-opportunity trials in the early stage disease setting are a potential means of expanding the collection of specimens for translational studies but the variability in surgical techniques and intra-operative adjunctive therapies would need to be standardized. Any involved centers would need to be accredited (as in ACOSOG trials).

International Trials and Collaborations

- The IASLC is a potential resource to facilitate the construction of a large international database for mesothelioma.
- International clinical trial groups that could collaborate with the NCTN include the Thoracic Alliance for Clinical Trials (TACT) based in Australia and the British Thoracic Oncology Group.

Trial Designs

- Trials for MPM conducted within the NCTN should generate new science and not develop a drug regulatory pathway, avoid replicating industry trials, be multidisciplinary, and include translational components.
- Molecular targets and drugs must be identified rapidly.
- Walk before you Run: To advance the field the initial trials should avoid complexity. There is a need establish feasibility, develop standards in the field, and demonstrate reproducibility in multiple centers.
- A number of potential designs for clinical trials were proposed and reviewed. The participants and panelists agreed that the two best trial designs to move forward at this time were a P/D ± IMRT trial and “Meso-MATCH”, an umbrella trial that shares features of NCI-MATCH with patient screening and assignment to any of several molecularly-targeted agents with specific relevance to MPM.

This Executive Summary presents the consensus arising from the CTPM. These recommendations are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research.

Anticipated Actions

The following manuscripts are under development:

- Mesothelioma CTPM consensus manuscript (meeting report, for July 2017 submission)
- Radiation oncology guidelines for post-EPP hemi-thoracic external beam radiotherapy versus IMRT, and post-P/D IMRT techniques (for August 2017 submission)
- Pathology and translational medicine standardization manuscript (for September 2017 submission)
- Surgical standardization guidelines manuscript (for October 2017 submission)
- Radiology guidelines for volumetric CT and modified RECIST in mesothelioma clinical trials (for November 2017 submission)
- Quality of life and patient-reported outcomes in mesothelioma; recommendations for clinical trial reporting (for February 2018 submission)

The following clinical trials are recommended for further development:

- P/D ± IMRT
- Meso-MATCH

References

1. S. J. Henley *et al.*, Mesothelioma incidence in 50 states and the District of Columbia, United States, 2003-2008. *Int J Occup Environ Health* **19**, 1-10 (2013).
2. S. D. Singh, S. J. Henley, A. B. Ryerson, Summary of Notifiable Noninfectious Conditions and Disease Outbreaks: Surveillance for Cancer Incidence and Mortality - United States, 2011. *MMWR Morb Mortal Wkly Rep* **62**, 11-51 (2015).
3. E. Taioli *et al.*, Determinants of Survival in Malignant Pleural Mesothelioma: A Surveillance, Epidemiology, and End Results (SEER) Study of 14,228 Patients. *PLoS One* **10**, e0145039 (2015).
4. T. Treasure *et al.*, Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol* **12**, 763-772 (2011).
5. L. M. Krug *et al.*, Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. *J Clin Oncol* **27**, 3007-3013 (2009).
6. E. Taioli, A. S. Wolf, R. M. Flores, Meta-analysis of survival after pleurectomy decortication versus extrapleural pneumonectomy in mesothelioma. *Ann Thorac Surg* **99**, 472-480 (2015).
7. T. Treasure *et al.*, The Mesothelioma and Radical surgery randomized controlled trial: the Mars feasibility study. *J Thorac Oncol* **4**, 1254-1258 (2009).

8. A. S. Tsao, R. Mehran, J. A. Roth, Neoadjuvant and intrapleural therapies for malignant pleural mesothelioma. *Clin Lung Cancer* **10**, 36-41 (2009).
9. N. J. Vogelzang *et al.*, Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* **21**, 2636-2644 (2003).
10. G. Zalcman *et al.*, Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet* **387**, 1405-1414 (2016).

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AGENDA

Day 1

8:30 – 8:35 a.m.	Welcome/introductions/goals of the meeting	Shakun Malik, Anne Tsao (co-chairs)
8:35 – 9:00	Overview of mesothelioma and SOC therapies	Anne Tsao

Early Stage

David Harpole, Harvey Pass (moderators)

9:00 – 9:15 a.m.	Surgical role of P/D and EPP	Bryan Burt
9:15 – 9:30	XRT advances IMRT	Ken Rosenzweig
9:30 – 9:45	Combining immunotherapy and XRT in mesothelioma	Daniel Gomez
9:45 – 10:00	Neoadjuvant XRT before resection	Marc de Perrot
10:00 – 10:15	Immune markers in early stage MPM	Aaron Mansfield
10:15 – 10:30	Lessons from the ICON study and application to mesothelioma	Boris Sepesi
10:30 – 10:45	Adjuvant WT-1 vaccine	Marjorie Zauderer
10:45 – 11:00	Surgery + intraoperative adjuvants	Joseph Friedberg
11:00 – 11:30 a.m.	Panel Discussion – Valerie Rusch (moderator)	

Panelists: Gideon Blumenthal, Raphael Bueno, Ritu Gill, Mary Hesdorffer, Andreas Rimner, and Charles Simone

Break – 15 minutes

Metastatic (Part 1)

Alex Adjei, Raffit Hassan (moderators)

11:45 – 12:00 p.m.	Exploitation of BAP1 abnormalities and mTOR therapies	Marjorie Zauderer
12:00 – 12:15	Developing immune-based treatments	Bruce Robinson
12:15 – 12:30	Update on immunotherapy trials	Anna Nowak
12:30 – 12:45	Mesothelin targeted agents	Raffit Hassan
12:45 – 1:00	CAR-T cell therapy for mesothelioma	Prasad Adusumilli
1:00 – 1:15	Anti-angiogenic therapy	Hedy Kindler

Break – 45 minutes

Metastatic (Part 2)

Alex Adjei, Raffit Hassan (moderators)

2:00 – 2:15 p.m.	ADI-PEG20	Peter Szlosarek
2:15 – 2:30	CDK4/6 inhibitors, FAK inhibitors	Dean Fennell
2:30 – 2:45	Targeting receptor kinases for mesothelioma	Ravi Salgia
2:45 – 3:00	Radiographic assessments of mesothelioma for trials	Ritu Gill
3:00 – 3:15	Trial design/defining accurate endpoints in clinical trials	Gideon Blumenthal
3:15 – 4:00 p.m.	Panel Discussion – Raffit Hassan, Shakun Malik (moderators)	

Panelists: Mary Hesdorffer, Harvey Pass, Tobias Peikert, Gideon Blumenthal, and Suzanne Dahlberg

Break – 15 minutes

Genomics and Preclinical Models

Suzanne Dahlberg, Shakun Malik (moderators)

4:15 – 4:30 p.m.	Genomics	Raphael Bueno
4:30 – 4:45	TCGA update	Julija Hmeljak
4:45 – 5:00	PDX models	Ming-Sound Tsao & Geoff Liu

Day 2

8:00 – 8:30 a.m. Epidemiology Overview Emanuela Taioli

Biomarkers

Fred Hirsch, Ravi Salgia (moderators)

8:30 – 8:45 a.m. Germline BAP1 and genetic interactions with the environment Michele Carbone

8:45 – 9:00 Recent findings on mesothelioma risk assessment studies Haining Yang

9:00 – 9:15 Plasma biomarkers Harvey Pass

9:15 – 9:45 a.m. Panel Discussion – **Tobias Peikert (moderator)**

Panelists: Michele Carbone, Suzanne Dahlberg, Geoff Liu, Ming-Sound Tsao, and Haining Yang

Break – 15 minutes

International Trials and Collaborations

10:00 – 10:15 a.m. Role of IASLC and mesothelioma Fred Hirsch

10:15 – 10:30 Role of NCI and mesothelioma Shakun Malik

10:30 – 10:45 a.m. Panel Discussion – **Fred Hirsch, Shakun Malik (moderators)**

Panelists: Marc de Perrot, Dean Fennell, Anna Nowak, Peter Szlosarek, and Ming-Sound Tsao

10:45 – 11:00 a.m. US patient referral base and enrollment to trials Mary Hesdorffer

Workshop Trial Designs and Action Items

11:00 – 1:00 p.m. Working Group – **Shakun Malik, Anne Tsao (moderators)**

Panelists: Raffit Hassan, Harvey Pass, Raji Sridhara, and Ed Korn

1:00 – 1:15 p.m. Wrap up and Conclusions **Shakun Malik, Anne Tsao**

Adjourn

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