

# Evolving Landscape of Initial Treatments for Patients with Malignant Pleural Mesotheliomas: Clinical Trials to Clinical Practice

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## Introduction

Mesotheliomas are a heterogeneous group of malignancies involving serosal surfaces comprised of distinct histologic subsets, including epithelioid, biphasic (mixed), and sarcomatoid. Malignant pleural mesothelioma (MPM) is the most common form of mesothelioma and the type most often studied in prospective clinical trials. Despite advances in our understanding of the molecular landscape of MPM,<sup>1,4</sup> there is still a paucity of prospectively validated biomarkers of response and resistance hindering our ability to tailor treatment regimens to a patient's cancer. Even with more than 2 dozen phase III trials, there have been few changes in patient outcomes and practice patterns with only 2 FDA approved treatment regimens, both of which are in the first-line setting: combination cisplatin/pemetrexed<sup>5</sup> and combination nivolumab/ipilimumab.<sup>6</sup> In this commentary, we will discuss the trials that have shaped the first-line treatment landscape for patients with advanced/unresectable MPM and provide perspective on the real-world integration of first-line immune checkpoint inhibitors (ICIs) into clinical practice.

## Cytotoxic Chemotherapy

Until recently, systemic cytotoxic chemotherapy was the *de facto* standard-of-care initial treatment option for patients with unresectable MPM. The EMPHACIS trial, evaluating cisplatin and pemetrexed vs cisplatin alone, noted a clinically meaningful improvement in outcomes with the combination (median overall survival [OS]: 12.1 vs 9.3 months, respectively), and ultimately led to FDA-approval of the combination.<sup>5</sup> Although cisplatin is preferable, many patients with MPM are not cisplatin candidates due to intercurrent medical comorbidities; studies have shown that carboplatin may be substituted for cisplatin in these patients.<sup>7,8</sup> Of note, neither of the above-mentioned regimens integrated cytotoxic maintenance chemotherapy.

The role of maintenance therapy after the completion of a platinum doublet has been the topic of extensive investigation, including in several negative trials to date.<sup>9-11</sup> The phase III MAPS trial, which added the vascular endothelial growth factor inhibitor (VEGFi), bevacizumab, to cisplatin and pemetrexed also included maintenance bevacizumab and found an OS (18.8 vs 16.1 months) and progression-free survival (PFS; 9.2 vs 7.3 months) benefit compared to platinum doublet alone.<sup>12</sup> However, this trial did not compare efficacy of treatment with or without the bevacizumab maintenance. The recently published phase II NVALT19 trial noted switch-maintenance gemcitabine after the completion of a platinum backbone significantly improved PFS compared with surveillance alone (6.2 vs 3.2 months, respectively), but data on OS have yet to be reported and further investigation in a randomized setting is warranted.<sup>13</sup> The phase II/III DENIM trial evaluating the role of allogeneic mesothelioma tumor lysate-loaded dendritic cell therapy (MesoPher) after completion of first-line chemotherapy is ongoing and results to date are unknown.<sup>14</sup>

## Integration of Anti-angiogenic Inhibition

The role of VEGFi's has also been evaluated in the first-line setting, most notably in the abovementioned MAPS trial which, while not FDA-approved, is listed as an initial treatment option in the National Comprehensive Cancer Network (NCCN) guidelines.<sup>12,15</sup> The use of tyrosine kinase inhibitors (TKIs) which inhibit VEGF, among other targets, has not yet been shown to have the same modest benefits. The phase 2 SWOG S0905 study integrating cediranib (a TKI with activity against VEGF and platelet-derived growth factor receptor [PDGFR]) with cisplatin and pemetrexed did not significantly improve OS or PFS over cisplatin and pemetrexed alone.<sup>16</sup> Furthermore, the recent phase III LUME-MESO trial evaluating nintedanib (a TKI with activity against VEGF, PDGFR,

Received: 1 March 2021; Accepted: 9 March 2022.

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and fibroblast growth factor receptor [FGFR]) in combination with cisplatin and pemetrexed failed to show a PFS benefit over chemotherapy alone.<sup>17</sup> As such, the only currently recognized VEGFi to be considered in the first-line setting is bevacizumab in combination with platinum and pemetrexed. Investigation into the utility of leveraging the immunomodulatory effects of VEGFi with ICI<sup>18</sup> is ongoing in the first-line setting with the currently accruing phase III BEAT-meso trial (NCT03762018) combining platinum, pemetrexed, and bevacizumab with atezolizumab.

## Targeted Therapies

With a growing understanding of the molecular landscape of MPM<sup>1,2,19</sup> there have been several investigations in the first-line setting evaluating potential targeted therapies in MPM. Most are focused on evaluating activity in previously treated patients.<sup>20-24</sup> Noteworthy completed and ongoing trials in the first-line setting include:

- (1) *NF2*: The phase II COMMAND trial evaluated the FAK inhibitor, defactinib, as maintenance after completion of platinum and pemetrexed leveraging preclinical work noting moesin-ezrin-radixin-like protein (merlin) deficiency, as seen in *NF2* mutant tumors, sensitized to FAK inhibition.<sup>25</sup> The trial failed to show OS or PFS benefits with the addition of defactinib maintenance compared with placebo, including when stratified by low versus high merlin expression.<sup>9</sup>
- (2) *ASS1*: Loss of enzymatic activity of argininosuccinate synthetase 1 (*ASS1*) is enriched in non-epithelioid subsets of MPM and leads to dependence on exogenous arginine.<sup>26</sup> In the randomized phase II trial by Szlosarek et al.,<sup>27</sup> it was noted that treatment with ADI-PEG20, a pegylated arginine deaminase that scours-free arginine, was tolerable and improved PFS compared to best supportive care in the later-line setting. Furthermore, the phase I TRAP trial found that the combination of ADI-PEG20 with cisplatin and pemetrexed in the first-line setting was tolerable.<sup>28</sup> Based on these findings, the phase II/III ATOMIC-meso trial is under way evaluating ADI-PEG20 combined with a platinum doublet vs platinum doublet alone focusing on the treatment of patients with non-epithelioid MPM (NCT02709512).
- (3) *Heat shock protein 90*: The phase Ib MESO-02 trial showed safety and potential benefit of the integration of the heat shock protein 90 inhibitor, ganetespib, with platinum/pemetrexed and a potential negative correlation with response and the presence of global loss of heterozygosity.<sup>29</sup>

Further integration of our growing understanding of potential molecular targets in mesothelioma and interrogation of targeted therapeutics in first-line treatment is needed.

## First-Line ICI

Immunotherapy has been extensively studied in the later-line setting for patients with MPM.<sup>30-38</sup> However, it was not until the recent phase III CheckMate 743 trial<sup>6</sup> that ICI was incorporated into the first-line setting. Checkmate 743 randomized patients with previously untreated and unresectable MPM to platinum and pemetrexed (chemotherapy) vs nivolumab

and ipilimumab (dual-ICI).<sup>6</sup> The dual-ICI cohort had better OS compared with the chemotherapy cohort (18.1 vs 14.1 months, HR = 0.74, 95% CI, 0.60-0.91). Grades 3-4 adverse events were found in approximately 30% of patients in both arms; however, more patients required treatment discontinuation in the dual-ICI arm (15%) compared with the chemotherapy arm (7.4%). These results led to FDA approval of dual-ICI treatment in the first-line setting.<sup>39</sup>

In a prespecified analysis by histology, which was a stratification factor for randomization, the OS benefit in non-epithelioid MPM was dramatic, 18.1 months for the dual-ICI cohort vs 8.8 months for the chemotherapy cohort (HR = 0.46, 95% CI 0.31-0.68). However, among patients with epithelioid MPM, which comprises approximately two-thirds of MPM tumors, there was no statistically significant survival advantage with dual-ICI vs chemotherapy (18.7 vs 16.5 months, HR = 0.86, 95% CI, 0.69-1.08) and a signal for an initial detriment in PFS with dual-ICI in the first 6 months. Although programmed death-ligand 1 (PD-L1) was not a prespecified stratification factor for randomization, sub-group analysis by PD-L1 expression was prespecified and demonstrated that patients whose tumors had PD-L1  $\geq$  1% had improved OS (HR = 0.69; 95% CI, 0.55-0.87) with dual-ICI while PD-L1 negative disease showed no benefit (HR = 0.94; 95% CI, 0.62-1.40).

CheckMate 743 is a practice-changing trial for the treatment of patients with MPM; however, there are several caveats to adopting dual-ICI as first-line treatment for patients with MPM:

- (1) The benefit for patients with epithelioid MPM is unclear: While there was meaningful improvement in OS for patients with non-epithelioid MPM treated with dual-ICI compared with chemotherapy, this was not the case in the epithelioid subset (which comprised 75% of the study population). For patients with epithelioid MPM, it is unclear what the appropriate sequence of treatments may be, and because of this unanswered question, the NCCN guidelines include a footnote, indicating that dual-ICI is preferred in non-epithelioid histology and an option for patients with epithelioid histology.<sup>15</sup>
- (2) The control arm in Checkmate 743 used a regimen inferior to the triplet therapy included in the NCCN guidelines: platinum, pemetrexed, and bevacizumab. Bevacizumab provides an incremental survival advantage over cisplatin and pemetrexed alone.<sup>12</sup> While the addition of a VEGFi would likely not have substantially altered the benefit among non-epithelioid patients, inclusion of bevacizumab for the epithelioid subset could have altered the results.
- (3) Since PD-L1 was not a prespecified stratification factor, unlike histology, we do not know if the results associated with PD-L1 expression are just a surrogate for histology. Further prospective analyses including consideration of a multivariate analysis of these findings accounting for epithelioid vs non-epithelioid histology would be useful to demonstrate that the potential signal of benefit observed among patients with PD-L1-positive tumors is not confounded by other prognostic variables.<sup>40</sup>
- (4) For the 26% of patients 75 years of age and older in CheckMate 743, there was no benefit of dual-ICI

compared with chemotherapy (HR = 1.02; 95% CI, 0.70-1.48). Therefore, the generalizability of the overall study results to elderly patients who disproportionately experience MPM may not be appropriate.

- (5) Resectability, or lack thereof, in MPM is difficult to define due to the diffuse nature of the disease and varied criteria among institutions. Nearly half of the patients in CheckMate 743 were reported as having stages I-III disease which are considered potentially resectable. Further details on how patients were deemed unresectable would be beneficial as the population most likely to benefit from dual-ICI is defined.

CheckMate 743 noted a striking benefit of dual-ICI in patients with non-epithelioid MPM. This differentiated response based on routinely available pathologic information (epithelioid vs non-epithelioid) represents a much-needed step toward a more refined approach for patient selection for systemic therapy. For patients with non-epithelioid histology, especially those under the age of 75, the use of first-line dual-ICI is preferable over platinum-based chemotherapy. However, in epithelioid MPM and patients 75 years or older, the benefit of first-line dual-ICI compared with chemotherapy has not been established. Further study should focus on refinement of selection criteria that drives toward the biologic underpinnings of response to ICI therapy.

Analogous to the treatment of non-small cell lung cancers (NSCLC), providers must devise a more personalized approach to address the biological and clinical heterogeneity of MPM. For too long, we have implemented treatment modalities using sweeping generalizations to all comers based off resectability; the definition of which, and staging techniques used, at times, is nebulous and not well annotated in prospective trials. Unresectable can mean many things, ranging from technically unresectable due to tumor stage to medically inoperable due to age/comorbidities and thus represents an incomplete description of a complex clinical decision. As we continue to learn more about genomic heterogeneity,<sup>1,2</sup> differential outcomes by histology,<sup>41</sup> and the potential roles of biomarkers of response to dual-ICI,<sup>42-46</sup> we must integrate these variables into prospective trials to continue refining treatment decisions. While combination treatment with nivolumab and ipilimumab was associated with clinical benefit, we still have only a nascent understanding of biomarkers of response to dual-ICI in MPM. While the CheckMate 743 trial did collect archival tumor samples at enrollment and 2 optional biopsies on treatment, no correlates were reported to date; future analyses of these samples to further refine our understanding of potential predictors of response are eagerly awaited.

### Future Directions of Immune Checkpoint Inhibition in the First-Line Setting

With the integration of nivolumab and ipilimumab in the treatment naïve setting, we must continue to integrate ICIs into the care paradigm using informed approaches. The phase III CONFIRM trial recently noted OS benefit compared with placebo when patients, particularly those with epithelioid histology, received nivolumab after progression on initial platinum/pemetrexed therapy; emphasizing the need, especially in epithelioid MPM, to further evaluate the proper sequencing of chemotherapy and immunotherapy.<sup>47</sup> The DREAM3R trial (NCT04334759) has launched to compare combination

chemo-immunotherapy with durvalumab to chemotherapy alone based off the recently published DREAM trial.<sup>48</sup> The BEAT-meso trial is currently evaluating the potential incremental benefit of adding VEGF inhibition to a chemo-immunotherapy backbone (NCT03762018). Multiple trials are also examining the safety and efficacy of incorporating ICIs into the perioperative management of MPM (NCT04162015, NCT03918252). Novel immunotherapeutic approaches remain vital to addressing ICI resistance or failure, and many promising constructs, such as mesothelin-directed chimeric antigen receptor T cells (NCT04577326),<sup>49,50</sup> trispecific mesothelin-engaging antibodies (NCT03872206), dendritic cell therapy (NCT02649829), genetically modified adenovirus (NCT03710876, NCT04013334), and VISTA (NCT04475523) antibodies, are under study.

### Conclusion

For the first time in nearly 2 decades, there has been an FDA approval in MPM allowing for the integration of first-line ICI.<sup>6,39</sup> As has often been the case in the treatment of patients with mesothelioma, the decision between first-line dual-ICI versus systemic chemotherapy involves the integration of a complex amalgam of several clinical factors, and our understanding of potential predictors of response is still relatively limited. With progress comes new questions and the need to re-evaluate trial design, stratification, and enhance our approaches to biomarker development. Integration of novel treatment paradigms, including combination chemo-immunotherapy, targeted agents, vaccines, and potential cellular therapeutics in the earlier-line setting are needed. Future trials should leverage our growing understanding of the histologic and molecular heterogeneity of mesothelioma and strive to develop companion biomarkers so patients can be matched to the treatments from which they will derive the most benefit.

### Funding

This work was partially supported by a National Cancer Institute Cancer Center Support Grant to Memorial Sloan Kettering Cancer Center (P30 CA008748). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

### Conflict of Interest

**Michael Offin:** PharmaMar, Novartis, Targeted Oncology, Bristol-Myers Squibb, Merck Sharp & Dohme, Jazz Pharmaceuticals (Other—personal fees); **Valerie W. Rusch:** National Institutes of Health/National Cancer Institute, Genelix, Inc., Genentech, (RF), DaVinci Surgery (Other), Bristol Myers Squibb (Other—non-financial support), NIH/Coordinating Center For Clinical Trials (Other—personal fees); **Andreas Rimner:** Varian Medical Systems, AstraZeneca, Boehringer Ingelheim, Merck, Pfizer, Research to Practice, Cybrea, More Health (RF), AstraZeneca, Merck, Research to Practice, Cybrea, More Health (Other—personal fees), Philips/Elektro (Other—non-financial support); **Prasad S. Adusumilli:** National Institutes of Health/National Cancer Institute, Department of Defense, Atara Biotherapeutics (RF), patent US20180251546A1 licensed to Atara Biotherapeutics, patent WO2018165228A1 pending, patent



CA3034691A1 pending, patent US20170172477A1 pending, a patent CA3007980A1 pending, patent AU2016316033A1 pending, patent EP1979000B1 issued (IP); **Marjorie G. Zauderer**: Atara, National Institutes of Health/National Cancer Institute, Department of Defense, Epizyme, Sellas Life Sciences, MedImmune, Polaris, Bristol Myers Squibb, Curis, Millennium/Takeda, GlaxoSmithKline (RF), Roche (Other—non-financial support), Aldeyra Therapeutics, Atara, GlaxoSmithKline, Millennium/Takeda, Novocure (Other—personal fees), Mesothelioma Applied Research Foundation, IBM (Other).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

## Author Contributions

Conception/design: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors.

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