Immunotherapy for Mesothelioma: Rationale and New Approaches

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Abstract: Therapeutic advancement for mesothelioma has been stagnant, with minimal treatment innovation in the past decade. Recently, however, immune checkpoint blockade (ICB) targeting the programmed death 1 and cytotoxic T-lymphocyte–associated antigen 4 pathways has revolutionized the treatment of multiple malignancies and shown promise in mesothelioma, with multiple agents now recommended in the salvage setting for advanced disease progressive on platinum-based chemotherapy. Studies of frontline chemoimmunotherapy and ICB combinations have also been encouraging, and both are likely to become integrated into the frontline treatment strategy for mesothelioma in the coming years. Other novel immunotherapy strategies, including chimeric antigen receptor T-cell therapy, are being investigated in mesothelioma. Although early studies have demonstrated the safety of multiple agents, further trials powered for efficacy are needed. In addition, enrolling patients in window-of-opportunity trials of ICB in resectable mesothelioma and biomarker-focused correlative studies will be critical to furthering the mechanistic understanding of ICB in mesothelioma, which in turn will help to uncover biomarkers of response and resistance in these patients.

Keywords
Chimeric antigen T-cell receptor, CTLA-4, immunotherapy, mesothelioma, PD-1, PD-L1

Introduction

Mesothelioma is a rare malignancy of the mesothelial lining that originates predominantly in the thoracic pleura. It is estimated to cause approximately 43,000 deaths worldwide annually, with 2500 to 3000 new cases occurring each year in the United States.[1-3] The majority of cases are attributable to asbestos exposure. Although the incidence of mesothelioma appears to be slowly decreasing in the United States, the incidence and mortality rates of mesothelioma have continued to rise in other parts of the world.[4,5] Furthermore, therapeutic advancement in mesothelioma has been stagnant. Combination chemotherapy with cisplatin plus pemetrexed (Alimta, Lilly), which imparts an objective response rate (ORR) of approximately 40% and median overall survival (OS) of approximately 12 months, remains the only systemic therapy approved by the US Food and Drug Administration (FDA) for advanced malignant pleural

mesothelioma (MPM).[6] Additions to this approach have thus far been disappointing. The anti–vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab imparts an absolute OS benefit of 2 months when combined with cisplatin plus pemetrexed,[7] and the multikinase inhibitor nintedanib (Ofev, Boehringer Ingelheim) demonstrates no benefit when combined with cisplatin plus pemetrexed.[8]

Immune checkpoint blockade (ICB) targeting the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) pathways has revolutionized the treatment of multiple malignancies. In addition, chimeric antigen receptor T-cell (CAR-T) therapy has transformed the treatment approach for relapsed/refractory leukemias and lymphomas and is now being explored in multiple solid tumors, including mesothelioma. In this comprehensive, clinically focused review, we explore the biological rationale for ICB in mesothelioma. We then highlight the reported clinical trial data for ICB in mesothelioma and summarize ongoing key phase 3 studies that will provide vital data on the clinical efficacy of ICB in mesothelioma. Lastly, we explore future directions of immunotherapeutics in mesothelioma, with a focus on neoadjuvant and adjuvant window-of-opportunity ICB studies and CAR-T therapy.

Biological Rationale for ICB in Mesothelioma

Given the proposed role of chronic inflammation from asbestos in MPM pathogenesis, MPM has long been postulated to be an "immune-active" tumor. Multiple studies corroborate this hypothesis and support the potential utility of immunotherapy in MPM. Preclinical models of mesothelioma in mice have demonstrated high levels of PD-L1 expression on both tumor cells and stroma.[9] Clinically, retrospective analyses of mesothelioma biopsy specimens have identified a high rate of PD-L1 positivity, ranging from 20% to 70%, that appears to be correlated with non-epithelioid histology and poor OS.[10-19] Multiple factors may explain this wide range of PD-L1 positivity, including differences in PD-L1 assays and heterogeneity of tumor PD-L1 expression. In addition, PD-L1 positivity appears to be increased in patients with non-epithelioid histology, which may drive further variance in positivity between studies. Furthermore, chemotherapy has been shown to increase PD-L1 expression on both tumor and infiltrating immune cells in MPM tumor samples, which likely also plays a role in the varying levels of PD-L1 expression observed in published retrospective analyses owing to inconsistency in the timing of specimen collection.[20]

Other markers of an immunologically active tumor microenvironment have been shown to correlate with prognosis in MPM. Pasello and colleagues found that sarcomatoid/biphasic histology was associated with increased CD8+ T-cell infiltration and PD-L1 expression, as well as aggressive pathologic features.[20] In addition, in a study of 275 patients with MPM, high levels of intratumoral regulatory T cells and myeloid-derived suppressor cells were correlated with significantly shorter progression-free survival (PFS) and OS.[21] Additional studies have demonstrated expression of other immune checkpoints in MPM tumor and pleural fluid specimens, including T-cell immunoglobulin and mucin protein 3 (TIM-3) and lymphocyte activation gene 3–encoded protein (LAG-3).[22,23] Furthermore, using NanoString analysis to assess expression of 800 immune-related genes in 87 MPM specimens, Patil and colleagues found that 59% of analyzed samples demonstrated a high level of expression of genes associated with an adaptive immune response, including B-cell and T-cell gene signatures.[24]

Intriguingly, unlike other immunologically active tumors with encouraging clinical data for ICB, such as melanoma and non–small cell lung cancer, MPM typically does not have a high tumor mutational burden.[25] That said, multiple studies suggest that MPM may harbor a large number of potentially immunogenic chromosomal rearrangements, novel gene fusions, and short deletions; these genomic alterations are difficult to detect via whole-exome sequencing.[25-27] In a single-center retrospective study of 28 MPM specimens, chromosomal rearrangements were identified in every tumor sample.[27] Furthermore, these rearrangements were found to have neoantigenic potential, with circulating T-cell clones responsive to these neoantigens identified in collected peripheral blood from a patient with MPM. Taken together, these data suggest a mechanistic rationale for the clinical utility of ICB in mesothelioma.

ICB in Advanced Mesothelioma

Single-Agent Checkpoint Blockade in the Subsequent-Line Setting

No proven salvage treatment regimens exist for patients with advanced mesothelioma that progresses on first-line platinum/pemetrexed combination chemotherapy. Results with single-agent chemotherapeutics such as gemcitabine and vinorelbine have been disappointing, with median OS not exceeding 6 months in small phase 2 studies.[28,29] Early-phase clinical trial data for single-agent anti–PD-1/PD-L1 and anti–CTLA-4 checkpoint blockade in this setting have been mixed. Although multiple single-arm phase 1/2 studies of anti–PD-1/PD-L1 monotherapy have demonstrated encouraging ORRs and median OS in platinum-refractory MPM, a recent randomized

phase 3 study comparing single-agent pembrolizumab (Keytruda, Merck) with single-agent chemotherapy in platinum-refractory advanced MPM did not achieve its primary endpoint of PFS.[30] Overall, this finding suggests that additional phase 3 clinical trial data, in addition to exploratory biomarker studies, are needed to identify the subpopulation of patients with MPM most likely to benefit from ICB. Furthermore, given the early encouraging results of both frontline chemoimmunotherapy and ICB combinations in untreated advanced MPM, the eventual role of anti–PD-1/PD-L1 monotherapy in the salvage setting is uncertain.

Tremelimumab. Single-agent anti–CTLA-4 therapy has not demonstrated efficacy in advanced platinum-refractory mesothelioma. Although initial single-center phase 2 studies of the anti–CTLA-4 agent tremelimumab showed the therapy to be safe and tolerable,[31,32] a subsequent multicenter placebo-controlled phase 2b study of 569 previously treated patients with advanced pleural or peritoneal mesothelioma (DETERMINE) demonstrated no survival benefit when tremelimumab was compared with placebo.[33] Single-agent anti–CTLA-4 therapy is no longer being investigated as a therapeutic strategy in mesothelioma.

Avelumab. The anti–PD-L1 agent avelumab (Bavencio, EMD Serono/Pfizer) has been studied in advanced platinum-refractory mesothelioma in a phase 1b expansion cohort of the JAVELIN solid tumor international multicenter study.[34] In this single-arm study, 53 patients with unresectable advanced platinum-refractory pleural or peritoneal mesothelioma received intravenous (IV) avelumab at 10 mg/kg every 2 weeks until progression or unacceptable toxicity. The ORR was 9%, with a disease control rate (DCR) of 58% and a median OS of 10.7 months. A trend toward improved ORR, PFS, and OS was noted in patients with PD-L1 positivity (defined as ≥5% expression on tumor cells). Treatment was well tolerated, with 9% of patients experiencing grade 3/4 treatment-related adverse events (TRAEs), and no single AE occurred in 5% or more of patients. No phase 3 studies of avelumab in advanced mesothelioma are ongoing at the time of this publication.

Nivolumab. Nivolumab (Opdivo, Bristol-Myers Squibb) has shown encouraging efficacy as monotherapy in platinum-refractory mesothelioma, and it currently carries a National Comprehensive Cancer Network (NCCN) category 2A recommendation in this setting. In a single-arm single-center phase 2 study of nivolumab in 34 patients with advanced MPM and progressive disease on 1 or more chemotherapy regimens, patients treated with nivolumab demonstrated an ORR of 24%, a 12-week DCR of 47%, and a median OS of 11.8 months.[35] Tumor PD-L1 positivity did not correlate with benefit. Similarly, in the nivolumab-only arm (n=63) of a multicenter randomized phase 2 noncomparative study of nivolumab vs nivolumab/ipilimumab (Yervoy, Bristol-Myers Squibb) in platinum-refractory MPM, an ORR of 19% was observed, with a 12-week DCR of 44% and a median OS of 11.9 months.[36] The majority of adverse events were low-grade, with grade 1/2 fatigue (40%), decreased appetite (22%), and nausea/vomiting (17%) the most common. Lastly, the Japanese single-arm multicenter phase 2 MERIT study investigated nivolumab monotherapy in 38 patients with advanced MPM who had progressive disease on 2 or fewer chemotherapy regimens, with a primary endpoint of ORR.[37] In this study, the ORR was 29%, the DCR was 68%, and the median OS was 17.3 months. PD-L1 positivity (defined as ≥1% tumor cell expression) trended toward an improved response (40% vs 8% with PD-L1 negativity) and improved survival (hazard ratio for survival, 0.542; 95% CI, 0.208-1.415). Grade 3 or higher TRAEs occurred in 32% of the patients, the most common being elevated lipase (12%), pneumonitis (6%), diarrhea (6%), increased amylase (6%), and increased γ-glutamyl transferase (6%). On the basis of these encouraging results, nivolumab monotherapy was approved in Japan in August 2018 for the treatment of advanced MPM that had progressed on prior chemotherapy.

Overall, although nivolumab monotherapy has appeared promising as salvage therapy in advanced mesothelioma, these studies have been small and nonrandomized. Phase 3 studies are needed to confirm the observed benefits. A multicenter double-blind placebo-controlled phase 3 study of nivolumab in relapsed pleural or peritoneal mesothelioma (CONFIRM; NCT03063450) has accrued, with results pending.

Pembrolizumab. Owing to encouraging phase 1/2 clinical trial data in chemotherapy-refractory mesothelioma, pembrolizumab carries an NCCN category 2A recommendation in this setting. In an MPM cohort of KEYNOTE-028, a phase 1b multicenter multicohort trial of pembrolizumab in patients with PD-L1–positive (defined as ≥1% tumor cell expression) solid tumors, 25 patients with advanced MPM who had failed or were ineligible for standard chemotherapy were given IV pembrolizumab at 10 mg/kg every 2 weeks until progression or unacceptable toxicity.[38] Therapy was well tolerated, with only 5 patients (20%) experiencing grade 3 TRAEs. No grade 4/5 TRAEs were observed. In addition, clinical efficacy was encouraging, with an ORR of 20%. Subsequent to this result, a phase 2 study of pembrolizumab in advanced pleural or peritoneal mesothelioma was conducted at the University of Chicago.[39] In this study, 64 patients

with advanced mesothelioma and progression on platinum-based chemotherapy but no more than 2 lines of systemic therapy were administered IV pembrolizumab at 200 mg every 3 weeks until progression or unacceptable toxicity. Co-primary endpoints of this study were ORR in both a PD-L1 status–unselected and a PD-L1–positive population, in addition to a determination of the optimal PD-L1 threshold for response. The ORR in the total study population was 22%, with a DCR of 63% and a median OS of 11.5 months. Treatment was well tolerated, with the most frequently observed grade 3 TRAEs being adrenal insufficiency (4.5%), pneumonitis (3%), and fatigue (3%). ORR and median PFS were significantly better in the PD-L1–positive patients, with ORR values of 7%, 25%, and 43% and median PFS values of 2.8, 4.1, and 4.9 months in patients with no, low-level (1%-49%), and high-level (≥50%) PD-L1 expression, respectively. However, no statistically significant improvement in median OS was observed when patients were stratified by low/none vs high PD-L1 expression. Investigating a nonclinical trial population, a retrospective analysis of 93 patients with advanced MPM treated with off-label pembrolizumab found an ORR of 18%, a median PFS of 3.1 months, and a median OS of 7.2 months for the full cohort. ORR and median PFS were improved in the PD-L1–high (≥50%) patient population, as well as in patients with non-epithelioid histology.[40]

Despite these encouraging results, a recent multicenter phase 3 study (PROMISE-meso), in which 142 patients with platinum-refractory advanced MPM were randomly assigned to IV pembrolizumab at 200 mg every 3 weeks or to chemotherapy with gemcitabine or vinorelbine, did not mean its primary endpoint of PFS.[30] Although ORR favored pembrolizumab (22% vs 6% with chemotherapy), no difference in median PFS or OS was observed, with a median OS of 10.7 months for pembrolizumab and of 11.7 months for chemotherapy. Further studies are therefore needed to determine the role of pembrolizumab in relapsed/refractory mesothelioma, as well as the optimal patient population most likely to benefit from this therapy.

Combination Checkpoint Blockade in the Salvage Setting

Combination ICB with anti–PD-1/PD-L1 plus anti–CTLA-4 therapy has also demonstrated encouraging efficacy in single-arm phase 2 studies in chemotherapy-refractory mesothelioma. In the single-arm phase 2 NIBIT-MESO-1 study, 40 patients with advanced pleural or peritoneal mesothelioma and progression on platinum-based chemotherapy received IV durvalumab (Imfinzi, AstraZeneca) at 20 mg/kg plus IV tremelimumab at 1 mg/kg every 4 weeks for 4 cycles, followed by durvalumab every 4 weeks for 9 cycles or until unacceptable toxicity/progression.[41] The primary endpoint of the study was immune-related ORR. Immune-related ORR was 28%; DCR was 65% and median OS was 16.6 months, with 62% of patients alive at 1 year. Baseline PD-L1 expression was not correlated with ORR, PFS, or OS. Grade 3/4 TRAEs occurred in 18% of the patients. Of these, increased aspartate transaminase/alanine aminotransferase (AST/ALT; 5%), anemia/thrombocytopenia/neutropenia (5%), and increased amylase/lipase (5%) were the most common.

Combination ICB with nivolumab plus ipilimumab has been investigated in the salvage setting in MPM in 2 separate phase 2 studies. In the single-arm single-center phase 2 INITIATE study, 34 patients with advanced MPM and disease progression on platinum-based chemotherapy were treated with IV nivolumab at 240 mg every 2 weeks plus IV ipilimumab at 1 mg/kg every 6 weeks for 4 cycles, followed by maintenance nivolumab for up to 2 years or until disease progression/unacceptable toxicity.[42] The primary endpoint was DCR at 12 weeks. An objective response was achieved in 29% of the patients. The DCR was 67% and the median OS was not reached, with a 1-year survival rate of 64%. Post-hoc analysis found that PD-L1 positivity (defined as ≥1% tumor cell expression) was associated with improved response and clinical benefit. The largest trial to date of nivolumab plus ipilimumab in platinum-refractory advanced MPM (MAPS2) was a noncomparative multicenter randomized study in which patients received nivolumab or nivolumab/ipilimumab.[36] Those randomized to nivolumab/ipilimumab (n=62) received IV nivolumab at 3 mg/kg every 2 weeks plus IV ipilimumab at 1 mg/kg every 6 weeks for 2 years or until disease progression/unacceptable toxicity. The primary endpoint was DCR at 12 weeks. The DCR at 12 weeks for the nivolumab/ipilimumab arm was 50%, with an ORR of 28% and median OS of 15.9 months. Combined post hoc analysis of PD-L1 expression in the 2 arms found an association between PD-L1 positivity and objective response but not with 12-week disease control, although a subgroup of patients with PD-L1 expression of 25% or greater appeared to have improved response and disease control compared with PD-L1–negative patients. No unexpected toxicities were observed in the nivolumab/ipilimumab arm, with 26% of patients experiencing grade 3/4 TRAEs. The most commonly observed grade 3/4 TRAEs were elevated AST/ALT (7%), elevated γ-glutamyl transferase (5%), and fatigue (5%). On the basis of these encouraging data from the INITIATE and MAPS2 studies, nivolumab plus ipilimumab has a category 2A NCCN recommendation as subsequent therapy for patients with advanced MPM that progresses on first-line chemotherapy.

Table 1. Enrolling and Recently Accrued Studies of Immunochemotherapy and Combination ICB in Treatment-Naive MPM

Identifier	Study Phase	N	Regimen	Study Design	Primary Endpoint	Study Status	Location
04153565	1	18	Pembrolizumab plus cisplatin/pemetrexed	Single-arm	Safety	Active, recruiting	Multicenter, Japan
02899195	2	55	Durvalumab plus cisplatin/pemetrexed	Single-arm	OS	Active, not recruiting	Multicenter, US
02784171	2/3	126	Cisplatin/pemetrexed (arm A) vs pembrolizumab plus cisplatin/pemetrexed (arm B) vs pembrolizumab (arm C, phase 2 only)	Multiarm, randomized	PFS (phase 2), OS (phase 3)	Active, recruiting	Multicenter, international
04334759	3	480	Durvalumab plus cisplatin/pemetrexed vs cisplatin/pemetrexed	Multiarm, randomized	OS	Active, not yet recruiting	Multicenter, international
02899299	3	605	Nivolumab/ipilimumab vs platinum/pemetrexed	Multiarm, randomized	OS	Complete; positive study result	Multicenter, international

ICB, immune checkpoint blockade; MPM, malignant pleural mesothelioma; OS, overall survival; PFS, progression-free survival.

Frontline Chemoimmunotherapy and Immunotherapy Combinations

Much as in non–small cell lung cancer, chemoimmunotherapy and ICB combinations are both being explored in the frontline setting in advanced MPM. Early results suggest great promise. The first frontline chemoimmunotherapy study to present results was the multicenter phase 2 DREAM study from Australia.[43] In this study, patients who had advanced unresectable treatment-naive MPM received durvalumab at 1125 mg together with cisplatin at 75 mg/m^2 and pemetrexed at 500 mg/m^2 every 3 weeks for 6 cycles, followed by maintenance durvalumab every 3 weeks for up to 1 year or until unacceptable toxicity/progression. The primary endpoint of this study was the 6-month PFS rate. The study met its primary endpoint, with a 6-month PFS rate of 57%. In addition, the confirmed ORR according to Immune Response Evaluation Criteria in Solid Tumors (iRECIST) criteria was 50%, with a DCR of 87%. Median OS was not reached, but the estimated 1-year OS rate was 65% with a median follow-up of 14.4 months. Grade 3 to 5 AEs occurred in 66% of the patients, and 15% experienced grade 3/4 immune-related AEs, although no single grade 3/4 immune-related AE occurred in more than 5% of patients.

A similarly designed single-arm multicenter phase 2 study based in the United States (PrE0505), in which 55 patients with advanced unresectable treatment-naive MPM received durvalumab plus platinum/pemetrexed for 6 cycles followed by up to 1 year of durvalumab maintenance, was presented at the virtual 2020 ASCO Annual Meeting.[44] The primary endpoint of this study was OS compared with historical control, with power to detect an improvement in median OS from 12 months (historical with platinum/pemetrexed) to 19 months. The study met its primary endpoint, with a median OS of 20.4 months (95% CI, 13.0-28.5 mo) and a 1-year OS rate of 70.4% (95% CI, 56.3%-80.7%). An ORR of 56.4% was observed, with a DCR of 96.4%. The regimen was well tolerated, with minimal grade 3/4 TRAEs, of which anemia (25.5%) and fatigue (7.3%) were the most common. Tumor mutational burden and pretreatment PD-L1 did not correlate with OS. Interestingly, exploratory analyses demonstrated neoantigen-specific T-cell expansion in multiple patients, and additional correlative studies from this trial are ongoing. With encouraging results from the phase 2 DREAM and PrE0505 trials, a phase 3 randomized international study (DREAM3R) comparing durvalumab plus cisplatin/pemetrexed vs cisplatin/pemetrexed in treatment-naive advanced MPM is posted and set to begin accrual in the fall of 2020 (NCT04334759). Other enrolling chemoimmunotherapy studies in treatment-naive advanced MPM are listed in Table 1.

Frontline combination ICB with anti–PD-1 plus anti–CTLA-4 is also being investigated in the first-line setting in advanced MPM, with positive results. The phase 3 CheckMate743 study randomized 605 treatment-naive advanced MPM patients to up to 2 years

of IV nivolumab at 3 mg/kg every 2 weeks plus IV ipilimumab at 1 mg/kg every 6 weeks or to 6 cycles of standard-of-care platinum/pemetrexed chemotherapy.[45] The primary endpoint of this study was OS. The trial met its primary endpoint, with a median OS of 18.1 months in the nivolumab/ipilimumab arm compared with 14.1 months in the chemotherapy arm (HR, 0.74; 95% CI, 0.60-0.91). OS improvement was primarily driven by the non-epithelioid subgroup, in which nivolumab/ipilimumab achieved a median OS of 18.1 months compared with 8.8 months with chemotherapy. The rate of grade 3/4 TRAEs was similar in both arms, at approximately 30%, although more patients in the nivolumab/ipilimumab arm had grade 3/4 serious TRAEs (15% vs 6%) and experienced TRAEs leading to treatment discontinuation (23% vs 16%). Of note, the study did not stratify patients by PD-L1 status, and further investigation is needed to determine if this and other biomarkers may predict response to nivolumab/ipilimumab in treatment-naive advanced MPM.

With encouraging data from the phase 2 DREAM and PrE0505 studies, as well as the phase 3 CheckMate743 study, it is likely that both chemoimmunotherapy and combination ICB will become integrated into the frontline treatment strategy of advanced MPM in the coming years. How this will affect the salvage treatment algorithm for MPM remains to be seen. In addition, continued investigation of biomarkers is needed to identify the patients most likely to benefit from an immunotherapy-centered treatment approach.

ICB in Peritoneal Mesothelioma

Although the aforementioned phase 2 and 3 studies of frontline chemoimmunotherapy and combination ICB include only patients with MPM, multiple subsequent-line ICB studies have also included patients with peritoneal mesothelioma (PeM).[33,34,39,41] However, given the rarity of this tumor type and the low numbers of patients with PeM accrued to these studies, it is difficult to evaluate selectively the efficacy of ICB in patients with PeM. That said, a biological rationale exists to support the efficacy of ICB in PeM. Mutation or copy number alterations in the gene encoding BRCA1-associated protein 1 (*BAP1*), a nuclear deubiquitinase involved in DNA repair, have been frequently reported in MPM and in more than 70% of patients with PeM.[46] Interestingly, an inflamed tumor microenvironment has been demonstrated patients who have PeM with *BAP1* loss compared with patients who have intact *BAP1,* with increased expression of PD-L1 among other checkpoints, such as LAG-3 and CTLA-4.[47] Given the high frequency of *BAP1* alterations in both MPM and PeM, further research is warranted to determine the utility of *BAP1* loss as a predictive biomarker for ICB response. In any case, given the encouraging data for chemoimmunotherapy and combination ICB in MPM, it is likely that these therapies will also be adopted into the treatment strategy for advanced PeM. In addition, multiple ICB studies that include patients with treatment-refractory PeM, including a study of nivolumab plus ipilimumab (NCT02834013) and atezolizumab (Tecentriq, Genentech) plus bevacizumab (NCT03074513), are ongoing.

Future Directions of Immunotherapy in Mesothelioma

ICB in Surgically Resectable MPM

Whether limited (stages I-III) MPM is truly an operable disease is the subject of controversy. That said, with increased experience at large referral centers, an aggressive tri-modality approach, consisting of neoadjuvant/adjuvant chemotherapy, macroscopic complete surgical resection via either pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP), and either standard hemithoracic or intensity-modulated radiotherapy (RT), is being increasingly deployed. Multiple small single-arm studies including patients with resectable epithelioid or biphasic MPM support the feasibility of this approach, with low rates of perioperative morbidity/mortality and encouraging survival.[48-50]

Window-of-opportunity studies that incorporate neoadjuvant/adjuvant ICB into this tri-modality therapeutic approach for resectable MPM are critically important, albeit challenging. Controversy over the definition of resectability, ideal surgical technique, proper sequencing of therapies, and classification of radiographic response, in addition to small sample sizes and the financial burden of correlative analyses, are but a few of the challenges to designing these studies. However, their significance from the standpoint of biomarker and mechanistic discovery cannot be overstated. Neoadjuvant ICB allows correlation of the clinical and radiographic pathologic responses. In addition, copious amounts of post-treatment resection tissue coupled with timed pre- and post-treatment blood draws allow an in-depth assessment of the tumor immune microenvironment and systemic immune response to ICB. Examples of such crucial analyses include pathologic assessment with IHC and multi-spectral immunofluorescence (mIF), tumor whole-exome sequencing, circulating cell-free tumor DNA (cfDNA) analysis, cytokine analysis, and single-cell RNA sequencing. These assays allow an assessment not only of the dynamics of the immune response but also of their functional consequences, which will enable rapid identification of the key biomarkers of response and resistance to ICB in MPM.

Although data have yet to be reported, multiple window-of-opportunity neoadjuvant/adjuvant studies of ICB

Table 2. Enrolling and Recently Accrued Studies of Neoadjuvant/Adjuvant Immunochemotherapy and Combination ICB in Resectable MPM

Identifier	Study Phase	N	Regimen	Study Design	Primary Endpoint	Study Status	Location
04162015	1	35	Neoadjuvant nivolumab plus cisplatin/pemetrexed × 2 cycles followed by P/D	Single-arm	Feasibility	Active, recruiting	MSKCC, US
04177953	2	92	Adjuvant platinum/pemetrexed vs nivolumab plus platinum/pemetrexed	Multiarm, randomized	TNT, safety	Active, recruiting	Multicenter, Germany
02707666	1	15	Neoadjuvant pembrolizumab, surgery, adjuvant cisplatin/pemetrexed	Single-arm	Biomarker discovery, safety	Complete	University of Chicago, US
03760575	1	20	Neoadjuvant pembrolizumab, image-guided surgery, adjuvant pembrolizumab plus cisplatin/pemetrexed	Single-arm	Safety	Active, not yet recruiting	University of Pennsylvania, US
02959463	1	24	Adjuvant hemithoracic RT followed by pembrolizumab (cohort 1),[a] palliative RT followed by pembrolizumab (cohort 2)	Multiarm, nonrandomized	Safety	Active, recruiting	MDACC, US
02592551	2	20	Neoadjuvant durvalumab (arm A) or durvalumab/tremelimumab (arm B) or no treatment (arm C)	Multiarm, randomized	Biomarker discovery	Active, not recruiting	Baylor Uni-versity, US
03918252	1/2	30	Neoadjuvant nivolumab (arm A) or nivolumab/ipilimumab (arm B), surgery, investigator-choice chemotherapy, optional RT, adjuvant nivolumab	Multiarm, nonrandomized	Feasibility, safety	Active, recruiting	Multicenter, US
03228537	1	28	Neoadjuvant atezolizumab plus cisplatin/pemetrexed, surgery, RT (post-EPP only), adjuvant atezolizumab	Single-arm	Feasibility, safety	Active, recruiting	Multicenter, US

[a]Protocol for cohort 1 of this study allows prior P/D, not EPP. Patients in cohort 2 must have received prior platinum/pemetrexed, and prior ICB is allowed. Planned hemithoracic RT and prior EPP are not allowed.

EPP, extrapleural pneumonectomy; ICB, immune checkpoint blockade; MDACC, MD Anderson Cancer Center; MPM, malignant pleural mesothelioma; MSKCC, Memorial Sloan Kettering Cancer Center; P/D, pleurectomy/decortication; RT, radiotherapy; TNT, time to next treatment.

in resectable MPM are ongoing and accruing (Table 2). The Southwest Oncology Group is nearing completion of a phase 1 study of neoadjuvant atezolizumab combined with cisplatin/pemetrexed for 4 cycles, followed by surgery with EPP or P/D, post-EPP RT, and 1 year of maintenance atezolizumab (NCT03228537). Translational correlatives from this study include mIF and IHC studies of resected specimens, in addition to RNA analysis. Combination ICB is also being investigated in the neoadjuvant setting in MPM. A multicenter phase 1/2 study is sequentially enrolling patients with resectable epithelioid or biphasic MPM to arms of neoadjuvant nivolumab or nivolumab

Table 3. Actively Enrolling Studies of CAR-T Therapy in Pleural and Peritoneal Mesothelioma

Identifier	Study Phase	N	Regimen	Study Population	Primary Endpoint	Study Status	Location
03054298	2	18	Lentivirus-transduced mesothelin-targeted CAR-T with or without cyclophosphamide via IV or IP delivery	Mesothelin-expressing lung adenocarcinoma, PeM, MPM; ovarian/fallopian tube and primary peritoneal cancer	Safety	Active, recruiting	University of Pennsylvania, US
02414269	1/2	179	Mesothelin-targeted CAR-T alone (arm A), or with cyclophosphamide (arm B), or with post–CAR-T pembrolizumab (arm C)[a]	Mesothelin-expressing MPD from MPM, breast or lung cancer[a]	Safety (phase 1), clinical benefit (phase 2)	Active, recruiting	MSKCC, US
03608618	1	15	IPe administration of mesothelin-targeted CAR-T	PeM; ovarian/fallopian tube and primary peritoneal cancer	Safety	Active, recruiting	NCI, US
03907852	1/2	70	Mesothelin-targeted CAR-T with or without lymphodepletion	Mesothelin-expressing MPM and PeM, cholangiocarcinoma, NSCLC, ovarian cancer	Safety (phase 1), ORR (phase 2)	Active, recruiting	Multicenter, US
02408016	1/2	20	WT1-targeted CAR-T together with cyclophosphamide lymphodepletion and aldesleukin	WT1-expressing NSCLC or MPM in patients with HLA-A*0201 expression	Feasibility, safety, T-cell persistence	Active, not recruiting	Fred Hutchinson Cancer Research Center, US
03638206	1/2	73	Variable depending on malignancy; mesothelin-targeted CAR-T for mesothelioma	Multiple cancers	Safety	Active, recruiting	Single-center, China

[a]All patients in the MPM cohort and phase 2 of this study (which will include only MPM patients) will receive post–CAR-T pembrolizumab.

CAR-T, chimeric antigen receptor T cell; HLA, human leukocyte antigen; IP, intrapleural; IPe, intraperitoneal; IV, intravenous; MPD, malignant pleural disease; MPM, malignant pleural mesothelioma; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; NSCLC, non–small cell lung cancer; ORR, overall response rate; PeM, peritoneal mesothelioma; WT1, Wilms tumor 1.

plus ipilimumab, respectively. In this study, neoadjuvant ICB is followed by surgical resection, adjuvant investigator-choice chemotherapy, optional RT, and 1 year of adjuvant nivolumab (NCT03918252). Key correlative analyses include pathologic assessment via mIF, whole-exome sequencing, cfDNA assessment, and single-cell RNA sequencing (scRNAseq). A similarly designed phase 2 study using durvalumab and tremelimumab is also ongoing (NCT02592551). These trials are of particular interest given the recent positive results from the phase 3 CheckMate743 study of combination ICB in advanced MPM, and they will help to further our understanding of the biological mechanisms of these therapies in MPM.

CAR-T in Mesothelioma

CAR-T therapies that target the CD-19 antigen have received FDA approval for the treatment of relapsed/refractory leukemias and lymphomas. Given this success, a similar approach of engineering cytotoxic T cells to target tumor-specific antigens is also being investigated in a plethora of solid tumors, including both pleural and peritoneal mesothelioma.

One such antigen being investigated as a CAR-T target in mesothelioma is mesothelin. Mesothelin is a cell-surface glycoprotein expressed at low levels on normal mesothelial cells but overexpressed in malignant cells in more than 90% of patients with epithelioid MPM and more than 50% of patients with non-epithelioid MPM.[51-53] Overexpression has been shown to correlate with poor survival.[54] Mesothelin-directed CAR-T therapies have demonstrated encouraging activity in both in vitro assays and in vivo xenogenic mouse models,[55-57] but they have yet to demonstrate significant efficacy in clinical trials. In a phase 1 study of a "second-generation" CAR that

expressed murine anti-mesothelin, epitope spreading with minimal clinical efficacy and an anaphylaxis event occurred in a patient with MPM. The anaphylactic event was believed to be related to the murine-based protein.[58] A subsequent phase 1 study of a lentivirus-transduced CAR-T targeting mesothelin demonstrated CAR-T expansion in peripheral blood and persistence in tumor tissue with minimal adverse events, but limited clinical activity.[58]

One alternative approach that may result in improved efficacy is regional intrapleural or intraperitoneal delivery of CAR-T therapy. Intrapleural administration of mesothelin-targeted CAR-T therapy was shown to induce greater T-cell activation and tumor eradication compared with IV delivery in an orthotopic mouse model.[59] Intraperitoneal administration of CAR-T therapy has demonstrated similarly encouraging results in murine models of peritoneal carcinomatosis[60,61] and in human studies as well. In a phase 1 dose escalation trial of autologous CAR-T therapy targeting mesothelin, 20 patients (including 18 with MPM) were treated with a single dose of CAR-T therapy following IV cyclophosphamide lymphodepletion.[62] No CAR-T related toxicities more severe than grade 1 were observed, and responses were seen in 7 patients (including 2 complete responses). That said, 14 patients with MPM in this trial received subsequent anti–PD-1 therapy. Although studies suggest that anti–PD-1 therapy may potentiate CAR-T efficacy,[63] it also confounds analysis of the CAR-T efficacy data from this trial.

Another protein being investigated as a CAR-T therapy target in MPM is fibroblast activation protein (FAP), which is widely expressed in multiple malignancies, including MPM. FAP-targeted CAR-T therapy has demonstrated efficacy in mouse tumor models,[64] and a recent small phase 1 study of intrapleurally delivered FAP-targeted CAR-T therapy demonstrated minimal toxicity with persistence of CAR T-cells in peripheral blood.[65] Still other approaches are seeking to enhance CAR-T therapy through co-expression of chemokine receptors[66] and proteins that inhibit immunosuppressive mediators[67] or through co-treatment with other immunomodulatory therapies, such as those targeting chemokine receptor 4 (CXCR4) and PD-1.[63,68,69] These strategies, however, are still primarily in the preclinical stage of development. A summary of actively enrolling CAR-T studies in pleural and peritoneal mesothelioma is presented in Table 3. Although multiple preclinical studies support the efficacy of CAR-T therapy in mesothelioma, extensive clinical trial data are lacking, and we are likely still many years removed from seeing these treatments applied in the clinic or even in randomized phase 3 studies.

Concluding Remarks

Although innovations in the systemic treatment of mesothelioma have been minimal over nearly 2 decades, immunotherapeutic approaches have great promise to change this situation. Both preclinical and early clinical evidence support the mechanistic rationale for CAR-T in mesothelioma, but trials adequately powered for clinical efficacy are still needed. ICB is already being used in the clinic for chemotherapy-refractory MPM, and data exist to suggest that both chemoimmunotherapy and combination ICB will become part of the frontline treatment strategy for MPM in the coming years. That said, exploratory correlative studies are needed to further the mechanistic understanding of ICB in mesothelioma, which in turn will uncover biomarkers of response and resistance in these patients.

Disclosures

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