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Use of Immune Checkpoint Inhibitors in Mesothelioma

Patrick M. Forde, MD[1]
Arnaud Scherpereel, MD, PhD[2,3]
Anne S. Tsao, MD[4,*]

Address
[1]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA
[2]Pulmonary and Thoracic Oncology Department, Univ Lille, CHU Lille, INSERM U1189 OncoThAI, F59000, Lille, France
[3]French National Network of Clinical Expert Centers for Malignant Pleural Mesothelioma Management (MESOCLIN), Lille, France
[*,4]Department of Thoracic/Head and Neck Medical Oncology, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd. Unit 432, Houston, TX, 77030, USA
Email: astsao@mdanderson.org

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Opinion statement

Recent advances in immunology have extended into the mesothelioma field. To date, only Japan has given regulatory approval to salvage nivolumab in chemo-refractory mesothelioma patients. The USA has included in the NCCN guidelines that pembrolizumab (in programmed death ligand 1 (PD-L1) immunohistochemistry (IHC)–positive patients) and nivolumab with or without ipilimumab (whatever the PD-L1 status is) are accepted salvage therapies. Based on the growing body of literature, it is anticipated that checkpoint inhibitors will receive regulatory approval in the USA and Europe soon for salvage therapy. Additional research efforts will determine whether earlier stage patients and frontline unresectable patients will benefit from the addition of immunotherapy to their treatment regimens. The realm of biomarker research has lagged behind in mesothelioma. In general, mesothelioma has less tumor mutation burden than other malignancies. Most of the single-agent salvage checkpoint inhibitor trials have shown a trend correlating higher PD-L1 immunohistochemistry (IHC) with responses. However, survival data remains immature and a larger number of patient outcomes are needed to ascertain the value of PD-L1 IHC as a predictive biomarker. Incorporation of translational studies in all immunotherapy trials and especially window-of-opportunity resectable studies should be supported and instituted in all future mesothelioma trials.

Introduction

Mesothelioma is considered an orphan disease with limited treatment options. Currently, the standard use of immunotherapies is limited to certain areas of the world as regulatory approval has lagged behind. Recently, in 2018, Japan was the first country to grant regulatory approval for the salvage use of nivolumab based on the "A phase II Study of Nivolumab" - A Multicenter Open-Label Single Arm Study in Malignant Pleural Mesothelioma" (MERIT) trial. The USA has updated the NCCN guidelines [1] to include as salvage options, nivolumab with or without ipilimumab, or pembrolizumab in programmed death ligand 1 (PD-L1)–positive malignant pleural mesothelioma (MPM) patients. However, neither the FDA nor the EMA has granted approval yet to any immunotherapies and it remains difficult in certain countries to obtain immunotherapies for mesothelioma patients. The remaining manuscript will discuss the ongoing immunotherapy efforts in mesothelioma and provide an analysis of the direction the field is moving towards.

Neoadjuvant immunotherapies

The current standard practice for patients with resectable malignant pleural mesothelioma (MPM) is to consider multi-modality therapy. However, even with aggressive tri- or bi-modality therapy, the median overall survival remains 17–25 months [2–9]. Further research is needed to improve survival outcomes for these patients. However, designing and conducting neoadjuvant studies is difficult and mandates coordinated efforts from a dedicated multidisciplinary organization. In addition, there remains significant controversy on the optimal surgery and techniques, ideal sequence of multi-modality therapy, and definition of a "resectable candidate." There are challenges to radiographic imaging and also defining endpoints for the clinical trials. From a scientific perspective, there remains a significant knowledge gap in identifying predictive and prognostic biomarkers for MPM.

There is a critical need for window-of-opportunity trials which will enable correlation of tissue/blood biomarkers with radiographic imaging and clinical outcomes. Window-of-opportunity trials have the advantage to facilitate discovery, have the potential for clearer biomarker analysis, and can be more quickly done with limited sample size. However, window-of-opportunity trials are high-risk, financially expensive due to biomarker research, challenging to enroll patients, and due to the small sample size requires a large therapeutic effect over a short period of time to be significant. As the short drug exposure time during neoadjuvant window-of-opportunity trials is unlikely to provide significant clinical benefit, it is suggested that maintenance therapy afterwards may be necessary. Currently, efforts are underway to identify agents that have a reasonable side effect profile that can be given for 1–2 years and can provide survival benefit. The immunotherapy agents are leading candidates at this time for this role.

Although there are no published results yet from neoadjuvant immunotherapy (PD1/PD-L1 inhibitors ± CTLA-4 inhibitors or chemotherapy) mesothelioma studies, it is hypothesized that adding in immunotherapy as part of neoadjuvant therapy (± maintenance) will activate T cells against any residual systemic disease [10]. Current trials are listed in Table 1. The Southwest Oncology Group is currently enrolling to a neoadjuvant trial (S1619, NCT03228537) with cisplatin-pemetrexed with atezolizumab, a

Table 1. Neoadjuvant immunotherapy trials

Agents in neoadjuvant immunotherapy trials	Phase	NCT	Target	Type	*N*	Primary endpoint
Durvalumab vs tremelimumab + durvalumab (Baylor)	II	02592551	PD-1 inhibitor vs PD-1 + CTLA4 inhibitor	Neoadjuvant	20	Biomarker modification
S1619 cisplatin-pemetrexed-atezolizumab (SWOG)	II	03228537	PD-L1 inhibitor + chemo	Neoadjuvant	24	Safety, feasibility
Pembrolizumab (U of Chicago)	Pilot	02707666	PD-1 inhibitor	Neoadjuvant	15	Safety, feasibility
Pembrolizumab (MDACC)	I	02959463	PD-1 inhibitor	Adjuvant with XRT	24	Safety, feasibility

PD-L1 inhibitor, in resectable MPM patients. The translational studies will include PD-1/PD-L1 IHC expression in tumor cells, serum cytokine analysis, and gene expression profiling of plasma. Two window-of-opportunity trials of pembrolizumab (NCT02707666) and a phase II of MEDI4736 or MEDI4736 with tremelimumab (NCT02592551) are open at specific institutions. Finally, a dual PD-L1/CTLA-4 inhibitor window-of-opportunity trial (NCT 02592551) is assessing biomarker modulation in tumor specimens.

In summary, multi-modality clinical studies in resectable MPM are critical to advance the field. Future challenges include identification of predictive and prognostic biomarkers, investment in exploratory genetic profiling, refinement of radiographic evaluations of response, and optimization of systemic therapy. Patients with resectable MPM should be encouraged to consider clinical trial enrollment.

Frontline chemo-immunotherapy

In the frontline setting, several trials are underway investigating immunotherapies in combination with chemotherapy and also against the standard of care chemotherapy. To date, the DuRvalumab with first-line chEmotherApy in Mesothelioma (DREAM) trial has been the only reported study at ASCO and IASLC 2018. DREAM is an Australasian Lung Cancer Trials Group and NHMRC Clinical Trials Centre, single-arm, open-label phase II trial of durvalumab with cisplatin-pemetrexed in patients with MPM. Patients were eligible if they had non-radiated measurable disease, were unresectable, had no prior systemic therapy for MPM, had an ECOG PS of 0–1, had no previous immunotherapy, and had no autoimmune disease or concurrent corticosteroids. PD-L1 immunohistochemistry status was not a required eligibility criteria. Patients were treated with 6 cycles of cisplatin-pemetrexed at standard doses with durvalumab (1125 mg Q3 weeks). Patients then received durvalumab for 1 year as maintenance therapy (17 cycles). Patients were enrolled in two stages and the modified Response Evaluation Criteria in Solid Tumors (RECIST) and modified immune RECIST criteria were used for tumor assessment. The primary endpoint was a progression-free survival (PFS) at 6 months.

In the first stage, 31 patients were enrolled and results were presented at ASCO 2018. The median PFS was 7.3 months (95% CI 5.8–11.0 months) and the 6-month PFS rate was 65%. This enabled the trial to move on to stage II recruitment. The updated results were presented at IASLC 2018 in 54 patients. The median PFS was 6.2 months and 57% of patients achieved PFS at 6 months. Forty-six percent of patients ($n = 25$) achieved a PR (modified RECIST) as the best response and 48% ($n = 26$) achieved a PR by immune-modified RECIST. Twenty-one patients had a stable disease as the best response. Of note, 2 patients had pseudoprogression within the first 10 to 15 weeks of therapy, followed by responses, which is the first time pseudoprogression was reported in a mesothelioma triplet trial. The data remains immature but the 1-year overall survival (OS) estimate was 65% at a median follow-up of 14.4 months. There were no new safety signals, although there were five deaths (one mesothelioma, one aspiration pneumonia, one myocardial infarction, one pulmonary embolism, and one acute respiratory arrest). There were 66% grade 3–5 adverse events and 15% ($n = 8$) grade 3–4 immune-related adverse events. Thirteen percent of patients ($n = 7$) required high-dose steroids or other immune suppression. The most common any-grade immune-related events were 20% renal impairment, 9% hypothyroidism, 4% increased amylase/lipase, 4% pneumonitis, 2% adrenal insufficiency, and 2% hyperthyroidism. There was only 1 patient each that had grade 3 or higher immune-related toxicity (increased lipase/amylase, adrenal insufficiency, and renal impairment). For all toxicities at any grade, the most common AEs were fatigue, nausea, constipation, neutropenia, rash, peripheral neuropathy, and tinnitus.

The preliminary results from the DREAM study indicate that the triplet regimen of durvalumab with cisplatin-pemetrexed can yield a high response rate in some MPM patients should be studied further. However, this regimen should not be considered standard of care yet and careful selection of patients, given the five deaths on trial, is needed.

There are other ongoing studies looking at triplet immunotherapy combinations for MPM, including pembrolizumab plus chemotherapy (NCT 2784171), as well as a PrECOG0505 study of cisplatin-pemetrexed and durvalumab (NCT02899195). Results from these trials are eagerly anticipated to further define the role of chemotherapy with immunotherapy in MPM. In addition to combination chemotherapy-immunotherapy regimens, the CheckMate743 (NCT 02899299) randomized 600 treatment-naïve MPM patients to nivolumab-ipilimumab (until progression or unacceptable toxicity) or platinum-pemetrexed for 6 cycles of therapy. This trial is collecting tumor tissue for PD-L1 IHC and additional analysis.

Salvage single-agent checkpoint inhibitor therapies

When standard first-line pemetrexed-platinum chemotherapy fails in malignant pleural mesothelioma (MPM), there are very limited options for these patients and no widely recommended therapy in this setting [1, 11–13]. In fact, routinely used drugs such as vinorelbine or gemcitabine did very poorly with disease control rates (DCR) below 30% after 12 weeks of

treatment and median overall survival (mOS) not exceeding 6 months [11, 14]. Potential value of immunotherapy was suggested in mesothelioma because of the major role of the immune system in its tumorigenesis [15, 16]. Immune checkpoint inhibitors (ICI) targeting PD-1 or its ligand PD-L1 [15, 16, 17••], but not *cytotoxic T lymphocyte-associated protein* (CTLA-4) [18•], exhibited promising results when used alone as salvage therapy after first-line chemotherapy. Recent translational studies have also supported potential sensitivity to PD-1 pathway blockade due to specific immunogenic neoantigens that may be present in mesothelioma [19].

Tremelimumab (anti-CTLA-4)

Studies of single-agent CTLA-4 blockade were ultimately disappointing. In the phase 2b DETERMINE study, the CTLA-4 antibody, tremelimumab, demonstrated no improvement in survival compared with placebo for patients with pleural or peritoneal mesothelioma that had been treated with one or two prior chemotherapy regimens [18•]. In contrast, initial studies of single-agent PD-1 pathway blockade have shown considerable promise.

Nivolumab (anti-PD-1)

In a single-arm phase 2 trial conducted in the Netherlands, 34 patients were treated with nivolumab 3 mg/kg IV every 2 weeks [20]. The primary endpoint of the study was disease control rate (DCR) at 12 weeks. Only one patient had received more than one prior line of chemotherapy and 82% of patients had epithelioid histology. The DCR at 12 weeks was 47% (16/34 patients, including a partial response in 8/34 patients and stable disease in 8/34); of note, a further three patients had initial disease flare followed by tumor regression suggestive of immune-related pseudoprogression. In a longer term follow-up, 13/34 patients had sustained clinical benefit having attained either a partial response (9/13) or prolonged stable disease lasting > 6 months (4/13). The median progression-free survival (PFS) was 2.6 months [2.23–5.49] and the median overall survival (OS) was 11.8 months [9.7–15.7]. Treatment-related toxicities were consistent with those reported previously with nivolumab. In this study, tumor PD-L1 expression did not correlate with positive therapeutic outcomes from nivolumab therapy.

The Japanese phase 2 MERIT study enrolled a total of 34 patients who had received either one ($n = 24$) or two ($n = 10$) prior lines of chemotherapy for pleural mesothelioma [21••]. The primary endpoint of the study was objective response rate (ORR) and patients received flat dose nivolumab 240 mg IV every 2 weeks. Among the patients enrolled, 79% had epithelioid histology and 59% had tumors the expressed PD-L1 ≥ 1%. The ORR was 29% (10/34) and DCR was 67%. The objective response (40% in PD-L1+ vs. 8.3% in PD-L1−), PFS (7.2 m vs. 2.9 m), and OS (17.3 m vs. 11.6 m) appeared enhanced for patients whose tumors expressed PD-L1 compared to those without PD-L1 expression; however, these differences did not reach statistical significance perhaps due to the small population size. Treatment was well tolerated. The results of the MERIT study led to the August 2018 approval in Japan of nivolumab for unresectable pleural mesothelioma that has progressed after prior chemotherapy. (See Table 2.)

Table 2. Selected monotherapy checkpoint inhibitor studies in salvage mesothelioma

Agent	NCT	Inhibitor type	Population	ORR (%)	DCR (%)	PFS (months)	OS (months)
Pembrolizumab (KEYNOTE-028) [17••]	02054806	PD-1	Second line	20	76	5.8	18
Pembrolizumab [22]	02399371	PD-1	Up to 2 prior therapies	22	63	4.1	11.5
Nivolumab (NivoMes trial) [20]	02497508	PD-1	1 prior therapy	24	50	3.6	NR
Nivolumab (MERIT) [21••]	n/a	PD-1	Up to 2 prior therapies	29.4	67.6	6.1	17.3
Avelumab (JAVELIN) [23]	01772004	PD-L1	Salvage, any line	9.4	57	4.3	NR

Pembrolizumab (anti-PD-1)

Pembrolizumab has demonstrated efficacy for patients with previously treated mesothelioma in a single-arm phase 2 study conducted at the University of Chicago [22]. This study enrolled 64 patients with previously treated pleural or peritoneal mesothelioma; 39% of patients had > 1 prior line of chemo, 77% of tumors had epithelioid histology, and 88% of tumors were pleural. The co-primary endpoints of the study were to evaluate the ORR in all patients and in patients with PD-L1-positive tumors and to determine the optimal threshold for PD-L1 positivity in relation to tumor response. Pembrolizumab was administered at a flat dose of 200 mg IV every 3 weeks and was well tolerated with no unexpected toxicities reported. In this study, 22% (14/64) of patients attained a partial response, 41% (26/64) had stable disease as best response for an overall DCR of 63%. The median duration of response was 11.7 months, median PFS was 4.1 months, and median OS reached 11.5 months. Two further patients who were treated past initial disease progression eventually had a partial response. Among 62 patients evaluable for baseline tumor PD-L1 expression, 55% (34/62) had PD-L1 ≥ 1%. ORR was significantly higher in patients with baseline tumor PD-L1 expression (ORR was 7%; 25% and 43% in PD-L1-negative; 1–49%; and ≥ 50%, respectively). In addition, PFS was prolonged in those patients with PD-L1 ≥ 50% expression compared to those with lower level or absent tumor PD-L1 expression.

Avelumab (anti-PD-L1)

In a phase 1b expansion arm of a multi-cohort study, 53 patients with previously treated pleural or peritoneal mesothelioma (median 2 prior lines of therapy) received avelumab 10 mg/kg IV every 2 weeks [23]. Characteristics of the population enrolled included epithelioid histology in 81% of patients and PD-L1 positivity (defined as ≥ 5% or greater tumor cell expression) in 37% (16/43) of evaluable patients. The ORR was 9.4% and 49.1% of patients had stable disease leading to overall DCR of 59%. Median PFS was 4.1 months (1.4–6.2) and median OS was 10.9 months (7.5–21). The ORR was 19% in patients

whose tumors had PD-L1 expression of ≥ 5% versus 7.4% in tumors with lower or absent PD-L1.

Ongoing studies

Several randomized phase 2 and 3 studies of single-agent PD-1 pathway blockade after prior chemotherapy for mesothelioma are ongoing including the placebo-controlled CONFIRM study of nivolumab in the UK (NCT03063450).

Salvage combination checkpoint inhibitor therapies

To date, three trials evaluating in mesothelioma a combination of anti-CTLA-4 (tremelimumab or ipilimumab) antibodies (Ab) and anti-PD-1 (nivolumab) or anti-PD-L1 (durvalumab) were recently reported. In a single-arm phase II trial ("NIBIT-MESO-1," NCT02588131) [24], the combination of intravenous tremelimumab (1 mg/kg) plus durvalumab (20 mg/kg) given every 4 weeks for 4 cycles, followed by maintenance durvalumab at the same dose and schedule for nine doses was tested as first- or second-line treatment for unresectable malignant pleural or peritoneal mesothelioma patients. This trial met its primary endpoint with 11/40 (27.5%) patients exhibiting immune-related (ir) partial response (median DOS: 16.1 months) and 25/40 (65%) ir-disease control, leading to a median ir-progression-free survival (PFS) of 8 months and mOS of 16.6 months (95% CI: 13.1–20.1). Baseline tumor PD-L1 expression had no predictive or prognostic value.

In a multicenter randomized non-comparative, open-label phase 2 (IFCT "MAPS-2"; NCT02716272) trial [25••], 125 ECOG PS 0–1 patients > 18 years old, with histologically proven MPM progressing after one or two lines including at least one pemetrexed-platinum chemotherapy and measurable disease (according to modified Response Evaluation Criteria in Solid Tumours (mRECIST) for mesothelioma), were recruited and randomized (1:1) to nivolumab (3 mg/kg/2 weeks) alone or combined with ipilimumab (1 mg/kg/6 weeks) given up to 2 years or until progression or unacceptable toxicity. Patients were stratified by histology (epithelioid vs non-epithelioid), treatment line (second vs third line), and chemosensitivity to pemetrexed-platinum. The primary endpoint (DCR after the first 12 weeks of treatment) was achieved in both arms: 50% with nivolumab + ipilimumab vs 44.4% with nivolumab, respectively. Objective responses rates (ORR) were 25.9% and 18.5%, respectively, consistent with prior PD-1/PD-L1 inhibitor studies. There was no unexpected toxicity but, as expected, all grade/or grade (G) 3–4 toxicities were less frequent with nivolumab (88.9%/12.7%) than with the combination (93.4%/26.2%). The most frequent G3 adverse events were asthenia; AST, ALT, or lipase asymptomatic. There were 0 and 3 (4.8%) toxic deaths, in the nivolumab and the combination arm, respectively. Noteworthy, these toxic deaths occurred only in the first months of the trial likely partially linked to a learning curve of the investigators in the diagnosis and management of immune-related side effects and only during the first months of treatment of the patients. Finally, survival data showed notable mOS of 11.9 (95% CI

6.7–17.7) months for nivolumab arm and of 15.9 months (95% CI 10.7—not reached) for nivolumab + ipilimumab arm after a median follow-up over 20 months. First ancillary analyses suggested that both regimens seemed more efficient (ORR and mOS) in PD-L1+ MPM patients and particularly in "high" PD-L1 expressers (> 25% positive tumor cells) with ORR = 71.4% with the combination and = 62.5% for nivolumab alone, respectively, than in PD-L1-negative tumors. PD-L1 tumor expression (with 1% or 25% tumor cell cut-off) could favor response and longer OS in the nivolumab arm, but did not influence OS of patients receiving the combo. However, this study was only achievable in about 80% of patients with enough tumor tissue remaining. Moreover, there were only few "very high" PD-L1 expressers (> 50%) compared to the literature [15, 16].

Another trial ("INITIATE"; NCT03048474) [26] similarly assessed the value of nivolumab (flat dose of 240 mg/2 weeks) plus ipilimumab (1 mg/kg/6 weeks up to four times) in MPM (85% of patients) or peritoneal mesothelioma patients (n = 34 evaluable subjects out of 36 eligible patients) progressing after at least one line of platinum-containing chemotherapy. The patients had measurable disease according to the mRECIST criteria, ECOG PS 0–1, and adequate organ function. The DCR at 12 weeks (same primary endpoint than in MAPS-2 trial) was 68% (95% CI 50–83%), including 10 (29%) patients with partial response and 13 (38%) with stable disease. Secondary endpoints were safety, ORR, DCR at 6 months, PFS, and mOS. This was a single-center, non-randomized, and smaller trial compared to the MAPS-2 trial but the tolerance and the efficacy results were quite similar. Immune-related adverse events were found in 33 (94%) patients; the most common adverse events were infusion-related reactions, skin disorders, and fatigue. There was no unexpected toxicity reported for this combination. Grade 3 treatment-related adverse events were reported in 12 (34%) patients but without toxic death. Positive tumor PD-L1 expression (≥ 1%) was observed in 15 (44%) patients and was significantly correlated with MPM response (p = 0.018).

In conclusion, immunotherapy appears to offer real hope for relapsing MPM patients with both phase II trials showing the value of nivolumab alone or plus ipilimumab in this setting. The MAPS-2 results supported a NCCN panel decision to recommend these regimens as options for second-/third-line therapy in relapsing MPM patients, as well the decision of the FDA to give an "orphan drug" status to nivolumab and nivolumab + ipilimumab in this setting [1]. However, many questions remain unanswered, and more data is required from randomized phase 2 or 3 trials to select the best candidates suited for ICIs (pretreated vs. frontline patients, biomarkers, tolerance, etc.) and to define the long-term survival benefit, as well as the optimal treatment regimen (anti-PD-1 monotherapy vs. ICI combination). In this goal, a randomized phase III trial ("CheckMate743"; NCT 02899299; n = 600) is currently assessing the benefit of nivolumab + ipilimumab versus standard frontline chemotherapy.

In summary, immunotherapies are being researched in all settings of mesothelioma. It is anticipated that regulatory approval for the checkpoint inhibitors will be forthcoming within the next year for salvage mesothelioma. Studies in the earlier stage disease and in the frontline unresectable patients in combination with chemotherapy or dual immunotherapy inhibition are underway and may provide additional options for mesothelioma.

Compliance with Ethical Standards

Conflict of Interest

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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Papers of particular interest, published recently, have been highlighted as:

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