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Review

Immunotherapy advances in pleural mesothelioma

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***Abstract*:** Mesothelioma is a rare cancer that carries a poor prognosis. This malignancy has had few therapeutic advances prior to the introduction of immune checkpoint inhibitors. Immunotherapy is now a cornerstone of first-line treatment for pleural mesothelioma and has been shown to provide clinical benefit for relapsed or refractory patients treated with prior chemotherapy. This review article will discuss key immunotherapy trials in the scientific literature, along with challenges in the application of this therapy. We will also discuss future areas of immunotherapy research in the treatment of mesothelioma.

Keywords: checkpoint inhibitors, immunotherapy, lung cancer, medical oncology, novel therapies

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Introduction

Pleural mesothelioma is a rare and aggressive malignancy arising from the mesothelial lining of the pleural cavity. It is closely associated with asbestos exposure and characterized by a long latency period of 30–40 years between exposure and development of mesothelioma.[1] Policies enacted in the 1980s and 1990s to restrict or ban the use of asbestos have contributed to a decline in the incidence of mesothelioma. However, the overall number of cases of mesothelioma remains stable in part due to an aging population, as mesothelioma rarely develops before the seventh decade of life.[1,2] Moreover, asbestos remains in use in many countries around the world, and non-occupational exposure to asbestos in the built environment remains a risk.[3]

While outcomes for mesothelioma remain poor with an average 5-year overall survival (OS) of 15%, the histologic subtype carries important prognostic significance.[4] The 2021 WHO classification defines three histologic subtypes of pleural mesothelioma: epithelioid, sarcomatoid, and biphasic, which comprises both epithelioid and sarcomatoid components.[5] Epithelioid mesothelioma represents 60% of cases and is associated with a more favorable prognosis. Sarcomatoid mesothelioma represents roughly a quarter of cases and has a more aggressive phenotype. Lastly, biphasic mesothelioma represents 15% of cases and is often more difficult to treat than epithelioid mesothelioma.[6]

The pathogenesis of mesothelioma is hypothesized to be related to chronic inflammation caused by asbestos fibers. In addition, macrophages unable to clear asbestos fibers produce reactive oxygen species, leading to DNA damage and subsequent malignant transformation.[7] The tumor microenvironment of mesothelioma includes tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells that allow for the evasion of immune detection and clearance.[8,9] Immune checkpoint inhibitors restore cytotoxic T cell activity against tumor cells. This class of medications has revolutionized the treatment of pleural mesothelioma.

Prior to the introduction of immune checkpoint inhibitors, the standard of care for systemic treatment of unresectable mesothelioma was the combination of platinum-based chemotherapy and pemetrexed. This regimen was established in a phase III study published in 2003. The combination of cisplatin and pemetrexed resulted in a response rate of 41% and median OS of 12.1 months, compared to cisplatin alone, which

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had a response rate of 17% and median OS of 9.3 months (hazard ratio (HR) 0.77, $p = 0.020$).[10] For over a decade, there was little advancement in this chemotherapy treatment paradigm. In 2016, the addition of targeted vascular endothelial growth factor inhibition to chemotherapy was described in the phase III MAPS trial. In this study, the addition of bevacizumab to chemotherapy improved median OS compared to chemotherapy alone (18.8 vs 16.1 months, HR 0.77, $p = 0.0167$). There was increased toxicity with higher rates of grade 3 or higher hypertension (23% vs 0% in the chemotherapy arm) and thrombotic events (5% vs 1% in the chemotherapy arm) with the addition of bevacizumab.[11] While bevacizumab has not been approved by the FDA or EMA for this indication, this regimen retains a category one recommendation from the National Comprehensive Cancer Network (NCCN) for frontline treatment of mesothelioma.[12]

Initial immune checkpoint inhibitor trials in mesothelioma

Early studies of immune checkpoint inhibitors in patients with refractory mesothelioma demonstrated low objective response rates but often durable responses. One of the first immune checkpoint inhibitor trials in mesothelioma was published in 2013: MESO-TREM was a phase II study of 29 patients with chemotherapy-resistant mesothelioma who received the anti-CTLA-4 monoclonal antibody, tremelimumab. The study had an overall response rate of only 7%.[13] Early studies with pembrolizumab, an anti-PD-1 monoclonal antibody, were more promising. KEYNOTE-028 (2017) was a phase Ib basket study of pembrolizumab in patients with select PD-L1–positive tumor types. In the mesothelioma cohort of 25 patients, around 70% of patients had stable disease or a treatment response with a median response duration of 12 months.[13] This was followed by the phase II study, KEYNOTE-158, of pembrolizumab in both PD-L1 positive and PD-L1 negative patients ($n = 118$) with previously treated mesothelioma. The objective response rate in this study was 8% with a median response duration of 14.3 months.[14] Importantly, durable responses were seen regardless of PD-L1 status.

One of the first studies investigating dual immune checkpoint inhibition was NIMBIT-MESO-1 (2018), a phase II trial of tremelimumab and durvalumab, an anti-PD-L1 monoclonal antibody, in patients with unresectable mesothelioma in the first- or second-line setting. The primary endpoint of the study was immune-related objective response, which was seen in 28% of patients with a median duration of response of 16.1 months. Immune-related disease control was seen in 65% of patients. In this study, tumor PD-L1 expression did not correlate with response rates, progression-free survival (PFS), or OS.[15]

Immunotherapy as first-line treatment for unresectable mesothelioma

In 2021, the landmark phase III trial CheckMate 743 would cement the use of immune checkpoint inhibition in first-line treatment of mesothelioma. CheckMate 743 randomized patients with previously untreated unresectable mesothelioma to nivolumab (anti-PD-1 monoclonal antibody) plus ipilimumab (anti-CTLA-4 monoclonal antibody) for up to 2 years or six cycles of platinum plus pemetrexed chemotherapy. The study met its primary end point of OS benefit with a median OS of 18.1 months in the nivolumab plus ipilimumab arm compared to 14.1 months in the chemotherapy arm (HR 0.74, 95% confidence interval (CI): 0.60–0.91, $p = 0.0020$).[16] The 3-year PFS was 14% in the nivolumab plus ipilimumab arm compared to 1% in the chemotherapy arm. Grade 3 or 4 treatment-related adverse events were reported at similar rates in both treatment groups (30%). Immune-mediated adverse events and infusion reactions occurred in a quarter of patients, with the majority being mild to moderate in severity. Subgroup analysis showed that median OS with nivolumab plus ipilimumab was similar between epithelioid and non-epithelioid subtypes (18.2 vs 18.1 months).[17] In contrast, patients with non-epithelioid histology randomized to chemotherapy had significantly worse outcomes compared to those with epithelioid histology (median OS 16.7 vs 8.8 months).[17] These data led to FDA approval of combination nivolumab plus ipilimumab in the first-line setting.[18] Table 1 provides a summary of key clinical trials in the frontline treatment of unresectable mesothelioma.

Real-world data on immunotherapy

Real-world data on the use of combination immune checkpoint inhibition support its efficacy in the treatment of mesothelioma. In a cohort of 119 patients from Australia treated with nivolumab plus ipilimumab, median OS was 14.5 months.[19] The cohort included patients treated with immunotherapy as first line (75%)

Table 1. Completed clinical trials for frontline treatment of unresectable mesothelioma.

Study name	Design	Treatment	Primary outcome	Grade 3–4 AE
Vogelzang et al. (2003)	Phase III *N* = 456	Cisplatin + Pemetrexed vs Cisplatin	Median OS: 12.1 mo in cisplatin + pemetrexed arm vs 9.3 mo in cisplatin alone arm (HR 0.77)	
DREAM (2020)	Phase II *N* = 55	Durvalumab + chemotherapy	PFS at 6 mo: 57% (95% CI: 44–70)	Most common: neutropenia (13%), nausea (11%), and anemia (7%)
CheckMate 743 (2021)	Phase III *N* = 713	Nivolumab + Ipilimumab vs Chemotherapy	Median OS: 18.1 mo IO arm vs 14.1 mo chemo arm (HR 0.74, 95% CI: 0.60–0.91) Non-epithelioid: 16.7 mo IO arm vs 8.8 mo chemo arm	30% IO arm vs 32% chemo arm
PrE0505 (2021)	Phase II *N* = 55	Durvalumab + Chemotherapy	Median OS: 20.4 mo (95% CI: 13.0–28.5)	66% of patients Most common: anemia (20%), hyponatremia (9%), fatigue (7%)
IND227 (2023)	Phase III *N* = 440	Pembrolizumab + Chemotherapy vs Chemotherapy	Median OS: 17.3 mo pembrolizumab + chemo arm vs 16.1 mo in chemo arm (HR 0.79, 95% CI: 0.64–0.98)	27% IO + chemo vs 15% chemo arm
BEAT-meso (2025)	Phase III *N* = 400	Chemotherapy + Bevacizumab ± Atezolizumab	Median OS: 20.5 mo chemo + bevacizumab + IO vs 18.1 mo chemo + bevacizumab (HR 0.84, 95% CI: 0.66–1.06)	55% chemo + bevacizumab + IO vs 47% chemo + bevacizumab

AE, adverse events; CI, confidence interval; HR, hazard ratio; IO, immunotherapy; OS, overall survival; PFS, progression-free survival.

and as second line or later. In this cohort, there was no statistically significant difference in OS based on histologic subtype. The rate of grade 3 or worse adverse events was 24%, with colitis as the most common adverse event.[19] Dumoulin et al.[20] described a cohort of 184 patients from the Netherlands treated with nivolumab plus ipilimumab. Median age in this cohort was 71 years and included a greater proportion of patients with Eastern Cooperative Oncology Group (ECOG) 1 or greater. In this real-world cohort, the overall response rate was 21.7%, and the median OS was 14.1 months. Grade 3 or 4 treatment-related adverse events were seen in 28% of patients.[20] Data from Switzerland describe outcomes of dual immunotherapy in a cohort of 109 patients.[21] Efficacy outcomes among patients treated in first-line setting were generally inferior to what was reported in the CheckMate 743 with an overall response rate of 21% versus 40%, median PFS of 6.5 versus 6.8 months, and median OS of 12.6 versus 18.1 months. The authors note outcomes for patients with ECOG ⩾2 were particularly poor, with a median OS of 2.4 months. Among patients treated in second-line or later settings, the overall response rate was 15%, and the median PFS was 2.8 months. Similar rates of treatment discontinuation due to treatment-related adverse events were seen as compared to CheckMate 743 (19% vs 21%).[21] In subgroup analysis, there was no difference in survival based on histology or PD-L1 expression. As expected, these real-world cohorts reflect a less fit patient population as they include more patients with ECOG 1 or 2, which may account for some difference in treatment outcomes. Rates of treatment-related adverse events in these real-world cohorts remained comparable to what was seen in CheckMate 743. These real-world data confirm the efficacy of nivolumab plus ipilimumab.

Immunotherapy in relapsed/refractory disease

The performance of single-agent immune checkpoint inhibition as second-line therapy was tested in several phase III clinical trials. CONFIRM (2021) randomized 332 patients to nivolumab versus placebo after progression on platinum-based chemotherapy. Nearly two-thirds of trial

Table 2. Completed clinical trials for relapsed/refractory unresectable mesothelioma.

Study name	Design	Treatment	Primary outcome	ORR
MAPS2 (2019)	Phase II non-comparative trial *N* = 125	Nivolumab; Nivolumab + Ipilimumab	12 week disease control: 40% nivolumab arm; 52% nivolumab + ipilimumab	17% nivolumab arm; 31% nivolumab + ipilimumab arm
INITIATE (2019)	Phase II *N* = 38	Nivolumab + Ipilimumab	12-week disease control: 68% (95% CI: 50–83)	38%
PROMISE-Meso (2020)	Phase III *N* = 144	Pembrolizumab vs single-agent chemotherapy (gemcitabine or vinorelbine)	Median PFS: 2.5 mo IO arm vs 3.4 mo chemo arm (HR 1.06, 95% CI: 0.73–1.53)	22% IO arm vs 6% chemo arm
KEYNOTE-158 (2021)	Phase II *N* = 118	Pembrolizumab	ORR: 8%	8%
CONFIRM (2021)	Phase III *N* = 332	Nivolumab vs placebo	Median PFS: 3.0 mo IO arm vs 1.8 mo placebo arm (aHR 0.67, 95% CI: 0.53–0.85) Median OS: 10.2 mo IO arm vs 6.9 mo placebo arm (aHR 0.69, 95% CI: 0.52–0.91)	11% IO arm vs 1% placebo arm

CI, confidence interval; HR, hazard ratio; IO, immunotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

participants had received at least two lines of treatment prior to enrollment. The primary endpoints were PFS and OS. Median PFS was 3.0 months in the nivolumab group versus 1.8 months in the placebo group (adjusted HR 0.67, 95% CI: 0.53–0.85, $p = 0.0012$). Median OS was 10.2 versus 6.9 months in the placebo group (adjusted HR 0.69, 95% CI: 0.52–0.91, $p = 0.0090$).[22] PROMISE-Meso was a phase III trial that randomized patients to pembrolizumab versus institutional choice single-agent chemotherapy (gemcitabine or vinorelbine) in relapsed patients with progression after platinum-based chemotherapy. There was no difference in the primary end point of PFS with a median PFS for pembrolizumab of 2.5 months (HR 1.06, 95% CI: 0.73–1.53, $p = 0.76$). However, the objective response rate was greater in the pembrolizumab arm compared to chemotherapy (22% vs 6%).[23]

Data for the use of dual immune checkpoint inhibition as subsequent therapy comes from several phase II clinical trials. MAPS2 randomized 125 previously treated patients to nivolumab alone or nivolumab plus ipilimumab. It is important to note that this trial was designed as a non-comparative trial and was not powered to detect a difference between the two arms. The primary endpoint was 12-week disease control. Both nivolumab monotherapy and combination nivolumab plus ipilimumab had positive results with disease control rates of 40% and 52%.[24] In contrast, INITIATE (2019) was a single-arm phase II study of nivolumab plus ipilimumab after progression on platinum-containing chemotherapy. Primary end point in this trial was also 12-week disease control. Of 34 treated patients, 29% had a partial response and 38% had stable disease, resulting in a disease control rate of 68% (95% CI: 50–83).[25]

For patients treated upfront with chemotherapy, subsequent treatment with immunotherapy has been shown to provide clinical benefit. Table 2 provides a summary of completed clinical trials in the relapsed or refractory setting.

Combination chemotherapy and immunotherapy

Several studies have investigated the use of combination chemotherapy and immunotherapy, although many of these studies were designed prior to the publication of CheckMate 743.

Pembrolizumab has been studied in combination with chemotherapy in previously untreated patients. KEYNOTE-A17 was a phase IB trial of

first-line pembrolizumab plus cisplatin and pemetrexed. In this trial, 11% of patients experienced dose-limiting toxicities during cycle 1, and 74% of patients had grade 3 or 4 treatment-related adverse events during the study.[26] IND227 was the phase II/III trial of pembrolizumab with chemotherapy in previously untreated patients, but allowed for cisplatin or carboplatin. Results from the phase III trial showed OS was significantly longer (17.3 vs 16.1 months, HR 0.79, 95% CI: 0.64–0.98, $p = 0.0324$) in the chemoimmunotherapy group compared to chemotherapy alone, although the difference in median OS was modest. A greater number of grade 3 or 4 adverse events was seen in the chemoimmunotherapy group (27% vs 15%). In the prespecified subgroup analysis, improved OS was seen with chemoimmunotherapy compared to chemotherapy alone, regardless of PD-L1 positive or negative status. There was a trend toward improved OS in the PD-L1 negative cohort. Response rates stratified by PD-L1 status were similar (64% in PD-L1 positive vs 59% in PD-L1 negative).[27] Nivolumab, another PD-1 inhibitor, has also been studied in combination with chemotherapy in the phase II JME-001 trial (2021). This trial of 18 patients showed an objective response rate of 78% and a disease control rate of 94%.[28]

Several trials have looked at the role of PD-L1 inhibitors in combination with chemotherapy. DREAM (2020) was a single-arm phase II trial of durvalumab with standard chemotherapy in previously untreated patients ($n = 55$). Durvalumab and chemotherapy were administered for up to six cycles, and durvalumab was continued as maintenance for up to 12 months. The trial met its primary endpoint with 57% of study patients achieving PFS at 6 months (95% CI: 44–70).[29] Testing the same regimen of durvalumab with platinum-pemetrexed chemotherapy followed by maintenance durvalumab, PrE0505 was another phase II trial, this time with a primary end point of OS. Median OS was 20.4 versus 12.1 months in a historical control of patients treated with cisplatin and pemetrexed (95% CI: 13.0–28.5, $p = 0.0014$).[30] These trials were the basis for the development of a phase III clinical trial, DREAM3R, which aimed to compare durvalumab with chemotherapy to the physician's choice of either standard chemotherapy or ipilimumab and nivolumab. The study closed early due to slow accrual, and results have yet to be published at the time of this review.[31]

BEAT-meso (2025) was a recently published phase III trial assessing the addition of atezolizumab to standard chemotherapy with bevacizumab. There was no statistically significant difference in OS between groups (median OS 20.5 months in the atezolizumab/bevacizumab/chemotherapy arm compared to 18.1 months in the bevacizumab/chemotherapy arm, HR 0.84, 95% CI: 0.66–1.06, $p = 0.14$). Median PFS was longer in the atezolizumab arm (9.2 vs 7.6 months), and quality of life metrics were maintained in the atezolizumab arm. Consistent with prior literature, patients with non-epithelioid histology benefited the most from the addition of atezolizumab. In the subgroup analysis by PD-L1 status, a significant OS benefit (HR 0.66, 95% CI: 0.46–0.95, $p = 0.027$) with atezolizumab/bevacizumab/chemotherapy was seen among patients with PD-L1 positive tumors but not in PD-L1 negative tumors (HR 1.02, 95% CI: 0.74–1.41).[32]

An ongoing phase III trial, eVOLVE-Meso, will be comparing volrustomig, a bispecific antibody targeting PD-L1 and CTLA-4, in combination with carboplatin and pemetrexed against the investigator's choice of platinum-pemetrexed or nivolumab plus ipilimumab in the frontline setting.[33]

Search for a predictive biomarker in mesothelioma

Despite the successes of immune checkpoint inhibition in the treatment of mesothelioma, nearly 20% of patients do not respond to nivolumab plus ipilimumab.[16] Efforts to define a biomarker to predict response to immunotherapy have been unsuccessful to date.

PD-L1 expression is predictive of response to immunotherapy in other tumor types.[34] Consequently, there have been many efforts to explore PD-L1 expression as a biomarker in mesothelioma. A 2022 systematic literature review of PD-L1 expression and clinical outcomes showed that in a majority of studies that used anti-PD-(L)1 therapies, there was no association between survival and PD-L1 tumor expression.[35] In the studies where anti-PD-(L)1 therapies were not specified to have been used, patients with tumors expressing PD-L1 generally had poorer survival. Heterogeneity in population characteristics, approaches to PD-L1 measurement, and differing PD-L1 cut-off levels between studies limits the interpretation of existing data across studies.[35]

In CheckMate 743, the exploratory subgroup analysis based on PD-L1 expression showed that patients with PD-L1-positive tumors had improved OS benefit with ipilimumab plus nivolumab over chemotherapy (HR 0.69, 95% CI: 0.55–0.87) compared to patients with PD-L1-negative tumors (HR 0.94, 95% CI: 0.62–1.40). Median OS with nivolumab plus ipilimumab when stratified by PD-L1 expression was similar between groups (18.0 months in PD-L1 positive vs 17.3 months in PD-L1 negative). For patients treated with chemotherapy, PD-L1-negative patients had improved survival outcomes.[16] In IND227, the PD-L1 negative subgroup had a trend toward improved OS with chemoimmunotherapy.[27] In contrast, subgroup analysis from BEAT-meso showed improved survival among PD-L1-positive patients treated with atezolizumab/bevacizumab/chemotherapy.[32] Ultimately, there is insufficient evidence at this time to support the use of PD-L1 status to select for immunotherapy treatment in mesothelioma.

Tumor mutational burden (TMB) is another notable biomarker. A higher TMB is predictive of immune checkpoint inhibitor response in patients with non-small cell lung cancer (NSCLC) and melanoma.[36–38] However, mesothelioma tumors generally have a low TMB of around two mutations per megabase.[39,40] CheckMate 743 included an exploratory analysis of TMB showing that high TMB was not correlated with higher OS.[17]

Research into the genomic landscape of mesothelioma has led to the understanding that this is a cancer characterized by inactivating mutations in tumor suppressor genes, most commonly BAP1. BAP1 plays a role in gene expression, regulating histone activity, apoptosis, and DNA replication and repair.[41] In the PrE05050 trial, no single gene alterations, including alterations in BAP1, were associated with improved response to chemoimmunotherapy.[30] Separately, CheckMate 743 included exploratory analysis of a four-gene inflammatory signature score (RNA sequencing of CD8A, STAT1, LAG3, and CD274). Median OS was 21.8 months in patients with a high inflammatory signature score versus 16.8 months in patients with a low score (HR 0.57, 95% CI: 0.40–0.82) in the nivolumab plus ipilimumab arm; no such predictive impact was seen in the chemotherapy arm.[17] There remains an urgent need for prospective data to identify clinically relevant genomic and transcriptomic biomarkers to guide treatment decision making.

As established in CheckMate 743, tumor histology has a differential impact on chemotherapy treatment outcomes, but no such difference was seen among patients treated with immunotherapy. Based on these findings, tumor histology is a defining characteristic in treatment guidelines from national organizations such as NCCN and ASCO. The more chemotherapy-resistant biphasic or sarcomatoid histologic subtypes are generally recommended nivolumab plus ipilimumab or chemotherapy plus pembrolizumab as first-line therapy. In patients with epithelioid histology, platinum-pemetrexed chemotherapy with or without bevacizumab, nivolumab plus ipilimumab, or combination chemotherapy with pembrolizumab are recommended as first line.[12,42] Treatment selection must also be guided by patient comorbidities and shared decision making.

Future trials in immune checkpoint inhibition

Building off the success of immunotherapy are several upcoming phase I trials that seek to combine immune checkpoint inhibitors with novel therapies. One example is the immunomodulatory agent, KFA115, alone or in combination with pembrolizumab.[43] Another agent, alintegimod, is a small molecule with immunomodulatory and anti-neoplastic properties being studied in combination with ipilimumab, followed by nivolumab monotherapy.[44] Lastly, HFB200301 is a tumor necrosis factor receptor 2 agonist antibody under investigation as a single agent and in combination with tislelizumab, an anti-PD-1 monoclonal antibody.[45]

Immune checkpoint inhibition is also being studied in combination with local therapies such as radiation. An ongoing phase I trial (NCT04897022) is investigating pembrolizumab administered with intensity modulated pleural radiation in unresectable pleural mesothelioma.[46]

Immunotherapy in surgically resectable disease

The role of surgery in the management of mesothelioma remains controversial. For patients with early stage disease, surgical resection, most often pleurectomy and decortication (P/D), may be considered.[12] While surgical resection has long been performed and was thought to be beneficial based on single-center outcomes, it was not until 2011 that it was studied in a randomized controlled trial.[47] The phase III MARS trial showed that extended pleurectomy decortication as part

Table 3. Ongoing clinical trials of immunotherapy in combination with cytoreductive surgery.

Study name	Design	Treatment			Primary outcome
		Neoadjuvant	Surgery	Adjuvant	
Neoadjuvant					
NCT05647265	Phase II	Nivolumab and ipilimumab × 2 cycles	Surgical procedure not specified	n/a	Surgery rate and progression-free survival
Perioperative					
NCT03760575	Phase I	Pembrolizumab × 2 cycles	Experimental image-guided radical pleurectomy	Platinum-pemetrexed chemo and pembrolizumab × 4 cycles followed by maintenance pembrolizumab for up to 2 years	Safety and feasibility
NCT05932199	Phase Ib/IIa	Arm 1: Durvalumab and tremelimumab × 3 cycles Arm 2: Durvalumab, tremelimumab, platinum-pemetrexed chemo × 3 cycles	EPP or P/D	Arm 1 and 2: Durvalumab and tremelimumab × 2 cycles followed by durvalumab alone for a total of 12 months	Recurrence-free survival

EPP, extended pleurectomy decortication; P/D, pleurectomy and decortication.

of trimodality therapy had worse survival outcomes compared to patients who did not undergo surgery.[48] This was followed by the phase III MARS2 trial, which studied the impact of P/D, a less morbid and less extensive operation, in combination with perioperative chemotherapy. In MARS2, patients who underwent surgery again had worse survival outcomes and more serious adverse events compared to chemotherapy alone. The majority of patients in the trial had epithelioid histology (86%). Those with non-epithelioid mesothelioma had worse OS with surgery and chemotherapy (epithelioid histology HR 1.12, 95% CI: 0.86–1.47 vs all other subtypes HR 2.66, 95% CI: 1.22–5.8, $p = 0.049$).[49] Given these data, patient selection remains crucial, and candidates should be evaluated at high-volume centers with expertise in the surgical management of pleural mesothelioma.[12]

Several early-phase clinical trials aim to study the role of immune checkpoint inhibition in combination with surgery (Table 3). An ongoing phase I trial (NCT03760575) is enrolling patients to be treated with perioperative pembrolizumab in combination with surgery and adjuvant chemotherapy.[50] Several other surgical trials are utilizing dual immune checkpoint inhibition. One example is the ongoing phase Ib/IIa trial (NCT05932199), which randomizes patients to neoadjuvant durvalumab and tremelimumab with or without chemotherapy, followed by cytoreductive surgery and adjuvant durvalumab and tremelimumab.[51] Another phase II study (NCT05647265) is investigating the neoadjuvant combination of nivolumab and ipilimumab followed by cytoreductive surgery in patients with non-epithelioid mesothelioma.[52] It remains to be seen if the addition of immune checkpoint inhibition will improve outcomes for mesothelioma treated with cytoreductive surgery.

Non-immune checkpoint inhibitor immunotherapy approaches

Dendritic cell vaccination is another strategy to harness the immune system for cancer treatment. Dendritic cells are a potent antigen-presenting cell and help to initiate and regulate the T cell immune response. Dendritic cell vaccination is an adoptive cell therapy that utilizes autologous monocyte-derived dendritic cells exposed to cancer antigens to stimulate an immune response against the tumor. Several early studies in mouse models and patients with mesothelioma showed promising results utilizing dendritic cells pulsed with autologous tumor material.[53–56] However, the use of autologous whole tumor cell lysate was logistically challenging to scale for a larger clinical trial. A phase I trial using dendritic cells pulsed

with allogenic tumor cell lysate generated from mesothelioma cell lines showed increased survival in a mouse model and increased anti-tumor T cell response. In this study, there was no significant difference in efficacy in mice treated with autologous or allogenic lysate-loaded dendritic cell immunotherapy.[57] Dendritic cell vaccination using allogenic tumor cell lysate was then applied in a first-in-human phase I clinical trial, including nine patients. The study demonstrated safety and feasibility along with promising clinical activity, albeit in a small study population.[57]

These studies provided the rationale for the phase II/III trial, DENIM (2024), which investigated dendritic cell vaccination using allogenic tumor cell lysate as a maintenance therapy after the completion of chemotherapy in patients with mesothelioma. The primary endpoint of median OS was not statistically different between the dendritic cell immunotherapy group compared to best supportive care alone (16.8 vs 18.3 months, HR 1.10, 95% CI: 0.77–1.57, $p = 0.62$). The dendritic cell therapy group did show a significant increase in the expression of T cell activation marker inducible costimulatory on CD4+ T cells and a greater number of CD4+ T cells expressing the proliferation marker Ki67. The authors note that there was an increased time interval from the start of chemotherapy to the first administration of dendritic cell therapy compared to the earlier phase studies; however, it is unknown what impact this may have had on the study results. Adverse events related to dendritic cell vaccination were generally mild and most commonly infusion-related reactions, such as fever, chills, and fatigue, and injection site reactions.[58]

Dendritic cell vaccination targeting Wilms' tumor protein (WT1) has also been of interest as WT1 is overexpressed in a variety of tumor types, including mesothelioma.[59] Data from mouse model experiments and early-phase clinical studies suggest WT1-mRNA dendritic cell vaccination may be feasible, safe, and demonstrate immunogenic activity.[60,61] Several ongoing phase I and II clinical trials are investigating the combination of immune checkpoint inhibition with dendritic cell vaccination.[62,63] Research in dendritic cell vaccinations has shown promise, but this therapy requires further rigorous study.

CAR-T cell therapy is another adoptive immunotherapy approach in early stages of development for mesothelioma. With CAR-T cell therapy, autologous or donor T cells are genetically modified to express a chimeric tumor cell antigen-specific receptor to trigger an immune response. While this strategy has had success in the treatment of many hematologic malignancies, it has been more difficult to translate to the treatment of solid tumors. Solid tumors often have heterogeneous tumor antigen expression and complex tumor microenvironments that are immunosuppressive and lead to difficulty in T cell infiltration.[64] Ideal targets for CAR-T cell therapy are tumor-specific antigens with limited expression in normal cells. Mesothelin (MSLN) has been one such target as it is upregulated in several solid tumor types, including mesothelioma. A phase I clinical trial of mesothelin-targeted CAR-T cell therapy delivered intrapleurally among patients with malignant pleural disease demonstrated safety and tolerability.[64] EVEREST-2 is an ongoing phase I/II study of a mesothelin-targeted CAR-T cell therapy in solid tumors with MSLN expression and HLA-A*02 loss of heterozygosity, a second target with the goal of preventing on-target off-tumor toxicity in normal cells.[65] Fibroblast activation protein is another target for CAR-T cell therapy that was suggested to be safe and feasible in a small phase I clinical trial.[66]

Lastly, oncolytic viruses are another emerging immunotherapy under investigation. Oncolytic viruses are engineered to selectively replicate in tumor cells and induce immunogenic cell death. Talimogene laherparepvec (T-VEC), derived from herpes simplex virus type 1 (HSV-1) and modified to express granulocyte–macrophage colony-stimulating factor (GM-CSF), was the first FDA and EMA-approved oncolytic virus for the treatment of advanced melanoma.[67] Like T-VEC, many oncolytic viruses under development are administered by intratumoral injection.[68] For the treatment of mesothelioma, ONCOS-102 is an intratumorally administered oncolytic adenovirus expressing GM-CSF that was studied in combination with chemotherapy in a phase I/II trial. The treatment was well tolerated with no increase in severe adverse events compared to the chemotherapy alone arm. Patients treated with ONCOS-102 and chemotherapy who had disease control were found to have increased immune cell infiltration within the tumor.[69] HSV1716 is another oncolytic virus that has been studied in a phase I/IIa trial in patients with pleural mesothelioma. In this study

of 13 patients, HSV1716 was administered through an indwelling intrapleural catheter and was well-tolerated with adverse events including pyrexia, influenza-like symptoms, and fatigue. An anti-tumor immune response was seen in some patients, as demonstrated by the detection of Th1 cytokines and novel anti-tumor IgG.[70]

Conclusion

Immunotherapy has become a cornerstone in the treatment of advanced pleural mesothelioma, particularly in chemotherapy-resistant non-epithelioid subtypes. Scientific advances are greatly needed to better predict which patients will respond to immune checkpoint inhibitor therapy to avoid unnecessary treatment-related toxicity. Despite the advances brought about by immunotherapy in the last 5 years, overall outcomes for mesothelioma remain poor, and treatment options are limited. Novel strategies to harness the host immunological response to target cancer cells are under active investigation and may provide benefit to patients in the future.

Declarations

Ethics approval and consent to participate

Ethics approval was not required for this review article. Consent to participate: Not applicable.

Consent for publication

Not applicable.

Author contributions

Annie L. Zhang: Conceptualization; Investigation; Visualization; Writing – original draft; Writing – review & editing.

Melinda L. Hsu: Conceptualization; Supervision; Validation; Visualization; Writing – review & editing.

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