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REVIEW

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Current status and progress in immunotherapy for malignant pleural mesothelioma

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Abstract

Malignant pleural mesothelioma (MPM) is a rare and aggressive malignant disease. Currently, the platinum doublet of pemetrexed and cisplatin is the standard first-line treatment for unresectable MPM. However, recent promising results of immunotherapy have markedly changed the landscape of MPM treatment. Further, the ongoing innovative therapeutic strategies are expected to expand the range of treatment options; however, several questions remain unanswered. First, establishing predictive biomarkers with high potency is urgently needed to optimize the patient selection process. Second, further exploration of the combination algorithm is expected to unveil more effective and safe regimens. Moreover, other dilemmas, such as the resistance mechanism of immunotherapy and the role of immunotherapy in perioperative settings, still warrant further exploration.

KEYWORDS

immunotherapy, mesothelioma, predictive biomarker

1 | INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare and aggressive malignant disease arising in mesothelial cells of the pleural surface.[1] Asbestos exposure may induce chronic inflammation and release DNA-mutagenic agents, which are widely regarded as the cause of MPM.[2,3] The incidence of MPM is predicted to increase in the next decade in developing countries.[4] As most patients are usually diagnosed at an advanced stage, few patients are eligible for surgery and the efficacy of radiotherapy is limited. Based on the results of the evaluation of mesothelioma in a Phase III trial with alimta and cisplatin (EMPHACIS), a Phase III trial, the platinum doublet of pemetrexed and cisplatin is employed as the standard first-line treatment for patients with unresectable MPM.[5] The addition of bevacizumab to the platinum doublet has been investigated in the MAPS trial, which revealed prolonged median overall survival (mOS) compared with the administration of the traditional platinum doublet alone.[6] As the clinical benefit of chemotherapy is still limited due to the intrinsic nature of chemoresistance of the tumor and the absence of approved therapy in the second-line setting, more effective therapies besides chemotherapy are urgently needed.

Recently, the tumor microenvironment (TME) of MPM has been assessed in several studies, which described the prevalence of immunosuppressive cell infiltration.[7] In this context, the efficacy and safety of immune checkpoint inhibitors (ICIs), such as inhibitors specific to programmed death-1 (PD-1), PD-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated protein-4 (CTLA-4), were elucidated. Owing to encouraging

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progress, the longstanding logjam in the treatment of MPM has been broken and a new foundation has been laid for future treatment. We collected and reviewed recent studies relevant to the immunotherapy of MPM and discussed the progress and challenges associated with such therapies.

2 | ICI IN UNRESECTABLE MPM

Chemotherapy with or without ICI treatment is recommended for MPM patients with Stage IIIb or IV, sarcomatoid subtype, or medically inoperable situation due to poor performance status (Table 1).[8,9]

2.1 | Single-agent immunotherapy

2.1.1 | PD-1/PD-L1 inhibitor

The binding of PD-L1 to PD-1 can suppress the downstream signal in T cells and reduce the cytotoxicity of T cells as well as promote T-cell apoptosis.[10] The clinical benefits of using PD-1/PD-L1 inhibitors have been confirmed in several tumors, such as lung cancer and melanoma. Based on the success of these clinical trials and the animative results of several preclinical studies, numerous studies have sought to assess the efficacy and safety of PD-1 or PD-L1 antibodies in MPM.

Pembrolizumab is a humanized monoclonal PD-1 inhibitor with proven efficacy for treating MPM in several trials. KEYNOTE-028 (NCT02054806), a nonrandomized, open-label, Phase Ib study, sought to assess the antitumor efficacy and toxicity of pembrolizumab in patients with PD-L1-positive advanced solid tumors.[11] A total of 25 patients with previously treated MPM were enrolled from 13 centers in six countries and administered pembrolizumab (10 mg/kg every 2 weeks) for up to 2 years or until confirmed progression or intolerable toxicity. The MPM cohort exhibited a disease control rate (DCR) of 72%, an mOS of 18 months, a partial response (PR) rate of 20%, and a median duration of response (DOR) of 12 months. To our knowledge, KEYNOTE-028 provided the first evidence of the potential clinical benefit of pembrolizumab as a second-line treatment for MPM, enlightening further clinical trials. KEYNOTE-158 (NCT02628067), an open-label, single-arm, Phase II trial, was conducted in patients with MPM who progressed after first-line treatment or were intolerant to traditional chemotherapy.[12] A total of 118 patients with pretreated MPM and biomarker-evaluable tumor samples were included in this study and intravenously administered pembrolizumab 200 mg every 3 weeks for up to 35 cycles. The primary endpoint was objective response per the response evaluation criteria in solid tumors (RECIST) version 1.1. This study was also designed to identify predictive biomarkers. Disappointingly, objective response was observed in only 10 patients (8%), and the mOS was dismal at 10 months (95% confidence interval [CI], 7.6–13.4 months). There was no significant difference in the overall response rate (ORR) between the PD-L1-positive group and the PD-L1-negative group. KEYNOTE-139 (NCT02399371) is an ongoing Phase II study whose aim is to evaluate the antitumor activity of pembrolizumab for pretreated MPM to ultimately enable an assessment of the predictive potency of PD-L1, which is the primary endpoint. The PROMISE-Meso trial was the first randomized Phase III trial to evaluate the efficacy of pembrolizumab as a second-line treatment. A total of 114 patients were randomized to receive pembrolizumab (200 mg once every 3 weeks) or institutional-chosen chemotherapy (gemcitabine or vinorelbine). Although associated with an improved ORR (22% in the pembrolizumab arm vs. 6% in the chemotherapy arm), pembrolizumab failed to improve either median progression-free survival (PFS) (2.5 months for pembrolizumab vs. 3.4 months for chemotherapy) or mOS (10.7 months for pembrolizumab vs. 11.7 months for chemotherapy) over single-agent chemotherapy.[13]

Nivolumab, another humanized monoclonal PD-1 inhibitor, had promising results in several trials. In the NivoMes trial, a prospective, single-arm, Phase II trial, nivolumab was administered every 2 weeks via intravenous infusion at a dose of 3 mg/kg to 34 previously treated patients with MPM, with a primary endpoint of DCR and secondary endpoint of ORR at 12 weeks. Of the 34 patients, 8 experienced both PR and stable disease (SD), resulting in a 12-week DCR of 47% (16/34). Further, the secondary endpoint, the 12-week ORR, was 24% (8/34), and one patient with SD at 12 weeks eventually achieved PR after 18 weeks, resulting in an overall ORR of 26% (9/34). The median DOR in this trial was also 7 months. Despite an unremarkable median PFS of 2.6 months, an mOS of 11.8 months still suggested that this therapy is promising. The Japanese Phase II trial, MERIT, enrolled 34 patients with MPM that is resistant or intolerant to chemotherapy ≤2 regimens. The primary endpoint, ORR, was 29%, which was evidently higher in PD-L1-positive patients (PD-L1 ≥ 1%) than in PD-L1-negative patients (PD-L1 < 1%), with ORRs of 40% and 8%, respectively. The median OS and PFS were 17.3 and 6.1 months, respectively.[14] To date, no pseudoprogression has been formally reported; however, one patient (3%, 1/34) continued to receive nivolumab treatment at 18 months after progressive disease (PD). At the latest 3-year follow-up update, eight patients survived for 3 years and seven patients remained alive before the data cut-off date (November 12, 2019).[14] This study confirmed the efficacy of nivolumab as a salvage therapy and led to the approval of nivolumab as a second-line treatment for MPM in Japan. Nivolumab as a monotherapy was first assessed in CONFIRM (NCT03063450), a randomized, placebo-controlled, multicenter Phase III

TABLE 1 Clinical trials using immunotherapy for patients with unresectable malignant pleural mesothelioma

NCT number	Trial name	Phase	Regimen	Primary endpoints	Line	No. patients	Status	Results
NCT02497508	NivoMes	II	Nivolumab	12W DCR	At least 2nd line or more	38	Completed	12W DCR, 47%
JapCTI-163247	MERIT	II	Nivolumab	ORR	At least 2nd line or more	34	Completed	ORR, 26%
NCT02716272	MAPS2	II	Nivolumab versus Nivolumab + Ipilimumab	12W DCR	At least 2nd line or more	125	Completed	12W DCR, 44% versus 50%
NCT03048474	INITIATE	II	Ipilimumab + Nivolumab	12W DCR	At least 2nd line or more	35	Completed	12W DCR, 68%
NCT03063450	CONFIRM	III	Nivolumab versus placebo	PFS/OS	At least 2nd line or more	332	Completed	PFS, 3.0 versus 1.8 months; OS, 9.2 versus 6.6 months
NCT02054806	KEYNOTE-028	Ib	Pembrolizumab	ORR	At least 2nd line or more	25	Active, not recruiting	ORR, 20%
NCT02628067	KEYNOTE-158	II	Pembrolizumab	ORR	At least 2nd line or more	118	Completed	ORR, 10%
NCT02991482	PROMISE-Meso	III	Pembrolizumab versus CT (gemcitabine or vinorelbine)	PFS	At least 2nd line or more	114	Active, not recruiting	PFS, 2.5 versus 3.4 months
NCT01772004	JAVELIN	Ib	Avelumab	ORR	At least 2nd line or more	53	Completed	ORR, 9%
NCT02588131	NIBIT-Meso-1	II	Tremelimumab + Durvalumab	ORR	At least 2nd line or more	40	Completed	ORR, 28%
NCT01649024	MESOT-TREM-2008	II	Tremelimumab	ORR	At least 2nd line or more	25	Completed	ORR, 7%
NCT01655888	MESOT-TREM-2012	II	Tremelimumab	ORR	At least 2nd line or more	29	Completed	ORR, 13.8%
NCT01843374	DETERMINE	IIb	Tremelimumab versus placebo	OS	At least 2nd line or more	571	Completed	OS, 7.7 versus 7.3 months ($p = 0.41$)
NCT02899299	Checkmate 743	III	Ipilimumab + Nivolumab versus CT	OS	First line	92	Completed	OS, 18.1 versus 14.1 months ($p = 0.0020$)
NCT02899195	PrE505	II	Durvalumab + CT	OS	First line	55	Completed	OS, 21.1 months
ACTRN 12616001170415	DREAM	II	Durvalumab	PFS rate at 6 months	First line	54	Completed	PFS rate at 6 months, 57%
NCT04334759	DREAM3R	III	Durvalumab + CT versus CT	OS	First line	480	Recruiting	—
NCT03762018	ETOP BEAT-meso	III	Atezolizumab + CT + bevacizumab versus CT + bevacizumab	PFS/OS	First line	320	Recruiting	—

Abbreviations: 12W DCR, disease control rate at 12 weeks; CT, chemotherapy; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

trial, whose results were released at the World Conference on Lung Cancer (WCLC). A total of 332 patients with refractory mesothelioma after at least one prior line of treatment were enrolled and randomly assigned (ratio 2:1) to receive either nivolumab or placebo treatment. The study met its co-primary endpoints, with improved median PFS (3.0 vs. 1.8 months, hazard ratio [HR], 0.62; $p < 0.001$) and mOS (9.2 vs. 6.6 months, HR, 0.72; $p = 0.02$) in the nivolumab group versus the placebo group. Subgroup analysis revealed a significant OS benefit in the epithelioid subtype; however, there was no clear correlation between OS and PD-L1 expression.[15]

Several other studies have assessed the activity of PD-L1 inhibitors, such as avelumab and durvalumab. In the JAVELIN Solid Tumor study (NCT01772004),[16] a Phase Ib, open-label clinical trial, avelumab (10 mg/kg, every 2 weeks) was administered to 53 patients with pretreated mesothelioma until disease progression or unacceptable toxicities. However, ORR, the primary endpoint of the study, was 9%, and the mOS was 10.7 (95% CI, 6.4–20.2) months. Pseudoprogression was identified in one patient (2%, 1/53) beyond PD and showed subsequent SD. In summary, the results of these small-sample studies using ICI monotherapy (NivoMes, MERIT, and JAVELIN) failed to surpass that of KEYNOTE-028, especially in OS and PFS. The NCT04115111 trial was designed to evaluate the effectiveness and safety of durvalumab as a salvage treatment for advanced previously treated MPM. The primary endpoint of the study was the proportion of patients who were alive and free from progression or death at 16 weeks, calculated from the start of treatment. The study was completed on May 16, 2019; however, the results have not been published.

2.1.2 | CTLA-4 inhibitors

CTLA-4 is an important immune checkpoint molecule that can downregulate T-cell response, mainly by competing for CD80/CD86.[17,18] Previous studies have demonstrated that the blockade of CTLA-4 can provide significant antitumor efficacy in MPM murine models.[19]

Tremelimumab, a fully humanized anti-CTLA-4 antibody, is by far the only anti-CTLA-4 agent that has been evaluated as a monotherapy in clinical trials for the treatment of MPM. The MESOT-TREM series studies included two open-label, single-arm, Phase II studies that sought to assess the efficacy and safety of tremelimumab as a second-line treatment for patients with unresectable malignant mesothelioma. In the initial MESOT-TREM-2008, patients received tremelimumab 15 mg/kg intravenously once every 90 days until PD or severe toxicity.[20] The primary endpoint was the proportion of patients who achieved an objective response. The targeted ORR value was 17% according to the modified RECIST; however, only two patients (7%) achieved PR and no patient is yet to experience complete response; the study thus failed to reach the expected value. The subsequent MESOT-TREM 2012 study (NCT01655888) intensified the administration schedule of tremelimumab. Overall, 52% patients achieved disease control, with a median duration of 10.9 months.[21] DETERMINE (NCT01843374), a Phase IIb, randomized, double-blind, placebo-controlled trial was performed with patients with unresectable malignant mesothelioma using tremelimumab as a second-line or third-line treatment.[22] A total of 571 participants were randomized to receive tremelimumab or placebo at a ratio of 2:1. No differences were found between the two groups in terms of OS, PFS, ORR, or DCR. Moreover, the treatment-emergent adverse events were relatively higher in the tremelimumab group than in the placebo group. Taken together, only tremelimumab treatment had limited therapeutic benefits in patients with MPM.

2.1.3 | T-cell immunoglobulin-3 (TIM-3) and lymphocyte activation gene-3 (LAG-3) inhibitors

The topography of the TME in MPM has recently been investigated. Besides the expression of PD-1, exhausted T cells have been found to upregulate various checkpoint molecules, including TIM-3, LAG-3, and V-type immunoglobulin domain-containing suppressor of T-cell activation (VISTA).[23,24]

TIM-3 is a member of the TIM gene family, and immunosuppressive TIM protein is expressed by T helper (Th) 1 and $CD8^+$ cytotoxic T cells. Several studies have shown that the expression of TIM-3 was high in tumor-infiltrating lymphocytes (TILs) in different tumors, including MPM.[24] Based on the promising results of preclinical studies, several clinical trials have been conducted to assess TIM-3 antibodies either as a monotherapy or a combination therapy with other ICIs for the treatment of several malignancies. An open-label, dose-escalation Phase I trial (NCT03652077) was initiated to evaluate the safety, tolerability, and efficacy of TIM-3 inhibitor (INCAGN02390) in select advanced tumors, including malignant mesothelioma. The trial is ongoing, with an estimated completion date of September 2021.

LAG-3 (CD223) is expressed on the surface of activated T cells, shares structural similarities with CD4, competitively binds to major histocompatibility complex type II (MHC-II) molecules expressed on antigen-presenting cells, and negatively regulates the proliferation and activation of antigen-specific T cells.[25] A Phase I trial (NCT03538028) evaluated the safety, tolerability, and efficacy of LAG-3 inhibitor (INCAGN02385) in select advanced tumors, including malignant mesothelioma. The trial has been completed; however, the results have not been released.

Several preclinical and clinical studies have shown that other immune checkpoints, such as VISTA, can serve as potential therapeutic targets for MPM.[26,27]

2.2 | Combination therapy

Synergic effects are commonly observed when an ICI is combined with chemotherapy or another ICI in many tumors. Such synergy applies to the treatment of MPM, as demonstrated by laboratory and clinical results.

2.2.1 | ICI-chemotherapy combination

The Australian DREAM study (ACTRN12616001170415), which is a multicenter, single-arm, open-label, Phase II trial, assessed the clinical outcome of combining durvalumab with pemetrexed-cisplatin as a first-line treatment for MPM, which led to promising results. As the primary endpoint, the PFS rate at 6 months was 57%, and the ORR, DCR, and mOS were 48%, 87%, and 18.4 months, respectively.[28] ICI combined with pemetrexed-cisplatin also met the primary endpoint, with an mOS of 21.1 months compared with the pemetrexed-cisplatin historical control of 12.1 months in PrE0505, a similar Phase II study.[29]

Based on the results of the DREAM study and PrE0505, DREAM3R/PrE0506 (NCT04334759), a Phase III trial, was recently initiated to evaluate the activity of durvalumab plus cisplatin-pemetrexed in previously untreated patients with MPM. The primary endpoint is OS, and the study is currently recruiting participants.

In the ongoing IND-227 Phase III study (NCT02784171), patients have been randomized (1:1) to receive pembrolizumab plus platinum–pemetrexed or platinum–pemetrexed. Another Phase III study, the ETOP BEAT-meso trial (NCT03762018), is currently recruiting patients to receive platinum–pemetrexed–bevacizumab with or without atezolizumab. Of note, the combination of ICI and chemotherapy is being evaluated as a first-line treatment in these studies.

2.2.2 | ICI–ICI combination

NIBIT-Meso-1 is an open-label, nonrandomized Phase II trial.[30] As a second-line or third-line treatment, tremelimumab (1 mg/kg) and durvalumab (20 mg/kg) were administered to 40 patients every 4 weeks for four cycles followed by maintenance with durvalumab for up to nine cycles. The results of this trial were encouraging, with an ORR of 28% and an mOS of 16.6 months. The Phase II MAPS2 trial (NCT02716272) was a multicenter, two-arm, noncomparative study.[31] A total of 125 patients with relapsed MPM were randomized (1:1) to receive either nivolumab or nivolumab plus ipilimumab. In this intention-to-treat population, the primary outcome of 12-week DCR was 40% and 52%, while the ORR was 17.5% and 25.8% in the monotherapy and combination therapy groups, respectively. The combination therapy group was found to have a slight OS benefit relative to the monotherapy group (mOS, 11.9 vs. 15.9 months), at the cost of increased Grade 3–4 toxicities. Moreover, a positive correlation was found between PD-L1 expression and ORR, especially in patients with PD-L1 ≥ 25%. The efficacy of the combination therapy was evaluated in another single-center, single-arm, Phase II study, INITIATE (NCT03048474),[32] which enrolled 38 patients with relapsed MPM after at least one line of platinum-based chemotherapy. The study met its primary endpoint, with a DCR of 68% in 34 patients with efficacy assessment at 12 weeks, including 10 and 13 patients with PR (10/34, 30%) and SD (13/34, 38%), respectively.

The landmark CheckMate-743 trial opened a new era in the immunotherapy of MPM.[33] CheckMate-743 is an open-label, randomized, multicenter, Phase III study. A total of 605 patients were randomly assigned (1:1) to receive standard platinum-pemetrexed chemotherapy for up to 6 cycles or nivolumab (3 mg/kg once every 2 weeks [q2w]) plus ipilimumab (1 mg/kg q6w) for up to 2 years. The study met its primary endpoints, with an mOS of 18.1 months in the ICI combo arm and 14.1 months in the chemotherapy arm. The benefits of nivolumab plus ipilimumab were consistently observed across both histological subgroups, as revealed by the similar mOS (18.7 months vs. 18.1 months), 1-year OS rate (69% vs. 63%), and 2-year OS rate (42% vs. 38%) between the epithelioid histology subgroup and non-epithelioid histology subgroup, respectively. Notably, a greater magnitude of benefit was observed in the non-epithelioid subgroup than the epithelioid histology subgroup, with an HR of 0.46, ultimately favoring nivolumab plus ipilimumab therapy. The significant improvement in OS and the acceptable safety profile led to the approval of this regimen as the standard care for previously untreated unresectable MPM in 2020 by the Food and Drug Administration (FDA).

The overexpression of LAG-3 and PD-L1 was previously observed in TILs in MPM. In preclinical models, a combination of LAG-3 and PD-1 blockade could facilitate a further increase in T-cell activity and a greater suppression of tumor growth relative to ICI monotherapy.[34] In clinical settings, the combined utilization of LAG-3 inhibitor (Ieramilimab) and PD-1 inhibitor (PDR001) has been assessed in a Phase I/II clinical trial (NCT02460224), which aimed to appraise the incidence of dose-limiting toxicities at 30 months in Phase I and evaluate the ORR per RECIST in Phase II. The trial was completed; however, the results are not yet available.

The coexpression of TIM-3 and other immune checkpoints has been described, which laid the foundation for combination therapy.

3 | ICI IN RESECTABLE MPM

For patients with early-stage MPM and the non-sarcomatoid type, surgery remains the first treatment; however, its curative effect is quite limited. Several

TABLE 2 Clinical trials with immune checkpoint inhibitors as a perioperative treatment for patients with resectable malignant pleural mesothelioma

NCT number	Phase	No. patients	Regimens	Primary endpoints	Status
NCT03918252	II/III	30	Arm A: preoperative Nivolumab only Arm B: preoperative Nivolumab + Ipilimumab	Safety and feasibility	Recruiting
NCT03228537	I	28	Neoadjuvant therapy with Cis-Pem-Atezo, surgery and maintenance with atezolizumab	Safety and feasibility	Activate
NCT02707666	I	15	Pembrolizumab 200 mg q3w, 3 cycles → Surgery → Cis-Pem 4–6 cycles → Pembrolizumab 200 mg 1 year (optional)	Gamma-interferon Gene expression profile (GEP) response rate; safety	Recruiting
NCT02959463	I	24	Cohort 1: Pembrolizumab 200 mg × 2 years after hemithoracic radiation therapy; Cohort 2: Pembrolizumab 200 mg × 2 years after palliative radiation therapy	Safety and feasibility	Recruiting
NCT02592551	II	20	Infusion of MEDI4736 (15 mg/kg intravenously, once), 1–6 weeks before surgical resection	Change in TME	Activate
NCT03760575	I	20	Pembrolizumab with image-guided surgery and chemotherapy	Safety	Not yet recruiting
NCT04177953	II	92	Carboplatin or cisplatin and pemetrexed + nivolumab: four cycles (q4w) of a combination of platinum-based adjuvant chemotherapy and immunotherapy	TNT and safety	Recruiting

Abbreviations: q3w, once every 3 weeks; q4w, once every 4 weeks; TME, tumor microenvironment; TNT, time to next treatment.

studies are ongoing to assess the safety and feasibility of ICI as a neoadjuvant, adjuvant, or perioperative therapy for resectable MPM. The details of these trials are presented in Table 2.

No related results have been reported to date for the efficacy and safety of ICI as perioperative therapy. Nonetheless, perioperative ICI therapy could downstage tumors to enable curative surgical resection in patients with initial unresectable MPM. Notably, patients with Stage I–II sarcomatoid MPM can obtain longer OS after surgery, but with more complications and higher mortality than those with non-sarcomatoid types. Thus, the role of surgery in sarcomatoid MPM is controversial.[35] As patients with the sarcomatoid subtype could benefit more from ICI treatment, patients with Stage I–II sarcomatoid MPM may benefit from perioperative ICI therapy.

4 | PREDICTIVE BIOMARKERS

4.1 | PD-L1 expression

Considering all related studies to date, PD-L1 expression has failed to be a powerful predictive biomarker for MPM. In the first randomized Phase III PROMISE-Meso trial, PD-L1 expression positivity did not lead to improved PFS or OS. In the landmark CheckMate-743 trial,[33] PD-L1 expression level was not robust enough to highlight prognostic differences between the PD-L1-negative and -positive group as PD-L1 was not a stratification factor in this study and the sample size of the PD-L1-negative population was relatively small. Consequently, PD-L1 is not considered a robust predictive biomarker for MPM due to multiple factors. First, a standard assay for PD-L1 testing has not been established because the antibodies used for immunohistochemistry in different studies are diverse. For example, CheckMate-743 used a 28-8 pharmDx assay (Dako), whereas the PROMISE-Meso trial used both SP263 and E1L3N clones to detect PD-L1 expression. Second, PD-L1 expression profiles may be affected by treatment; thus, the time point of biopsy operation counts for numerous. In most studies, biopsy was conducted before treatment; however, in some studies, biopsy specimens were obtained during treatment.[32] Altogether, there are still problems related to technology and study design that must be urgently solved.

4.2 | Histology type

Morphologically, MPM is classified into three subtypes: epithelioid, sarcomatoid, and biphasic. The histology type is a potential prognostic index for guiding treatment decisions. The mOS was 19 months for the

epithelioid subtype, 12 months for the biphasic subtype, and 4 months for the sarcomatoid subtype of MPM.[36] Thus, the epithelioid subtype is associated with a better prognosis and chemotherapy response.[36] The correlation between histology type and clinical outcome of immunotherapy has been reported. A positive outcome of ICI treatment was reported in patients with non-epithelioid type in several studies, such as the MESOT-TREM 2012, NivoMes, MERIT, and CheckMate-743 studies, while the opposite was reported in other studies, including the MESOT-TREM2008, CONFIRM, MAPS2, and DREAM. Such discrepancy may be attributed to the difference in the type of ICI or therapy lines.

4.3 | TME

The TME has been evaluated as an alternative predictive biomarker for immunotherapy. Researchers have suggested that the TME type may affect the outcome of immunotherapy. A comprehensive immune-proteogenomic analysis defined two disparate TMEs, TiME-I and TiME-II, which are also called good-TiME and bad-TiME. The good-TiME subtype is characterized by a greater number of PD-1$^+$CTLA-4$^+$CD8$^+$ T cells, whereas the bad-TiME subtype contains more Tregs and naive CD8$^+$ T cells. The good-TiME was reported to be associated with a better response to ICI as revealed in the BWH cohort, TCGA cohort, and COSMIC database.[37] In another study, the TME was classified into three groups based on NanoString analysis for 800 immune-associated genes. Based on the classification, Group 1 was desert-like and had poor immune-associated gene expression; Group 2 had moderate T-cell effector gene expression and high level of B-cell gene expression, and Group 3 had high PD-L1 expression with high T-cell effector gene expression. These comprehensive studies indicate the potential predictive value of the TME for MPM immunotherapy.[38]

4.4 | Other biomarkers

Genome analysis studies have revealed that the most frequent gene defect is loss-of-function mutations of tumor suppression genes instead of tumor driver genes.[39–41] As a result, the tumor mutation burden (TMB) has been reported to be low in MPM. Similarly, the prevalence of high-grade microsatellite instability (MSI-H) or deficient mismatch repair protein (dMMR) in MPM is low.[42] In very few studies, TMB was evaluated to predict the outcome of ICI leading to a negative result.[12] The findings of such studies may be the reason that TMB and dMMR/MSI-H are not good candidate biomarkers. Another study found breast cancer gene 1-associated protein-1 (BAP-1) as a robust and easily trackable predictive biomarker for peritoneal mesothelioma immunotherapy. Overall, patients with BAP-1 haploinsufficiency could benefit more from ICIs.[43]

5 | CHALLENGES AND PROSPECTS IN MPM IMMUNOTHERAPY

Although the rapid development in immunotherapy has opened up a new era of MPM treatment, there are still some critical challenges.

First, there is currently no reliable predictive biomarker. Although a correlation was found between the histological type and immunotherapeutic efficacy,[33] its underlying mechanism needs to be elucidated at the molecular level. In addition, upfront immunotherapy has markedly advanced the management of non-epithelioid MPM, and the best scenario to maximize the benefit of epithelioid MPM is far from being decipherable. According to current evidence, the proportion of people who can benefit from immunotherapy is limited, suggesting the existence of primary drug resistance. For example, in some studies, early PFS drop-off was observed in the ICI arms, such as in the CheckMate-743 study. Similar to other tumors, even among patients with an initial response, more than 70% develop secondary drug resistance. The critical direction to solve drug resistance in the future is to clarify the mechanism of drug resistance, set criteria for classification according to the corresponding mechanism, and provide corresponding treatment. Genome-wide association studies (GWAS) have found that single nucleotide polymorphisms in PD-L1 or CTLA-4 could predict the corresponding ICI response. Furthermore, studies on pharmacogenomic markers have found that genomic alterations in phosphatase and tensin homolog and human leukocyte antigen play a key role in ICI response.[44–46] The cost of dual ICIs is burdensome to both individuals and society. Therefore, it is urgent to identify predictive biomarkers for selecting potential responders. TME, as mentioned above, is a potential predictive biomarker. However, the complexity of TME makes it difficult to be elucidated by detecting the known immunotherapy-associated factors.[47] For example, transcriptomic data are intrinsically unable to show the abundance of proteins subjected to posttranslational control.

Second, treatment with anti-PD-1 plus anti-CTLA4 has been successful in mesothelioma; however, the control group in the Checkmate743 study received pemetrexed plus platinum without bevacizumab. Therefore, it is uncertain whether dual-immune combination therapy is superior to platinum-containing chemotherapy plus antiangiogenesis therapy. Population screening is needed to deliver more accurate treatments in more appropriate patients. In addition to this dual-immune combination, clinical trials of anti-PD-L1 inhibitors combined with other treatments are ongoing, and some have shared promising preliminary results, such as the combination of immunotherapy with chemotherapy or antiangiogenesis therapy.[28,29] Further exploration of anti-PD-L1-based treatment regimens and an optimal

set of biomarker combinations suitable for different therapies will be a major challenge. Moreover, the combination of chemotherapy and ICI exerts a synergic effect, which may increase the number of responders.[48,49] More specific studies are needed to determine how chemotherapy alters the immune environment and to obtain the best combination algorithm as well as the rationale timing of administration. Similarly, there are challenges in other potential combination strategies and the elucidation of the inner interaction mechanism, including the combination of ICI and other therapeutic strategies, such as TME-related immune regulatory drugs, antimetabolism drugs, antiangiogenic drugs, and tumor vaccines.[50]

Third, surgery or radiation therapy is not commonly used to treat mesothelioma. However, with the emergence of ICIs, perioperative treatment strategies for other tumors have gradually been changing. More patients who are not eligible for local treatment are likely to regain the chance to receive surgery or radiation therapy, which may prolong survival. Inspired by the encouraging studies of ICIs as first-line therapy, several trials using ICIs as a neoadjuvant therapy are ongoing, and their results are anticipated.

6 | CONCLUSION

The promising results of immunotherapy have markedly changed the landscape of MPM treatment. Ongoing innovative treatment strategies are expected to expand the range of treatment options. With the upfront change in ICI, there is an urgent need to establish predictive biomarkers to select patients in a targeted manner. The combination algorithm is expected to provide more effective and safe regimens for the treatment of MPM.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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