Mesothelioma and Immunotherapies

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Malignant pleural mesothelioma (MPM) is an asbestos-related cancer with a poor prognosis. Outcomes for MPM have not dramatically improved over the past 20 years due to its highly aggressive nature, the heterogeneity of the disease, the spectrum of histological subtypes and the limited therapeutic advances. Recently, immune checkpoint inhibitors (ICIs) have improved the outcomes in multiple malignancies, including a subset of MPM cases in the second-line setting and beyond, and more recently in the first-line setting. This article discusses the recent paradigm shift in MPM treatment with the addition of ICIs to the first-line treatment setting, based on the results of the Checkmate 743 study, which investigated ipilimumab plus nivolumab versus platinum-based chemotherapy (PC), and the Keynote 483 study, which investigated the addition of pembrolizumab to PC chemotherapy versus PC chemotherapy alone. We discuss the impact of ICIs on clinical outcomes in patients with MPM based on histological subtype and explore currently available biomarkers that may correlate with improved response to ICIs. Finally, we discuss future directions for improving MPM outcomes with tailored therapies based on therapeutic vulnerabilities and novel biomarkers.

Keywords

Immune checkpoint inhibitors, immunotherapy, malignant pleural mesothelioma, mesothelioma, neoplasms, glandular and epithelial, pembrolizumab

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Highlights

- Immunotherapy, especially combinatory immunotherapy, has shown promise with prolonged survival for patients with advanced mesothelioma in the first-line setting (see the sections on 'Systemic treatment and immunotherapy debut' and 'Randomized immunotherapy trials of mesothelioma').
- Histology-based therapy is important to consider, with non-epithelioid subtypes responding better to immunotherapy than to chemotherapy (see the section on 'Randomized immunotherapy trials of mesothelioma').
- The results of prospective clinical trials for single-agent immune checkpoint inhibitors (ICIs) in pleural mesothelioma have been somewhat inconsistent, but they have shown some possible survival advantages. This may be related to the heterogeneous nature of mesothelioma or unidentified biological differences that could predict the benefit of ICIs (see the sections on 'Randomized immunotherapy trials of mesothelioma' and 'Predictors of response to immune checkpoint inhibitors').
- Further biological insights are being tested with new combinations targeting various biological pathways of importance for mesothelioma survival (see the section on 'Future directions').

Malignant pleural mesothelioma (MPM) is a highly aggressive tumour that originates from the pleural serosal surface.[1] Asbestos exposure is the primary risk factor, and measures to reduce occupational asbestos exposure 30 years ago have decreased MPM incidence in developed Western countries.[2–4] In March 2024, the Environmental Protection Agency formally banned asbestos use in the USA. However, it will take many years to completely phase out its use. Asbestos, therefore, remains a health issue, and cases may continue to rise due to the long latency period between exposure and diagnosis of mesothelioma.[5] MPM is categorized into three main histological subtypes based on the 2021 World Health Organization classification: epithelioid, which constitutes 50–60% of cases and has a more favourable prognosis than the sarcomatoid subtype; sarcomatoid, which accounts for 10% of cases and tends to be more aggressive and resistant to chemotherapy; and biphasic, which exhibits epithelioid and sarcomatoid features and accounts for the 30–40% remaining cases.[6] Comprehensive genomic and transcriptomic sequencing of MPM has revealed molecular heterogeneity, loss of tumour suppressor genes and mutations in DNA repair genes, including breast cancer gene 1 (BRCA1)-associated protein 1 (*BAP1*), cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) and neurofibromatosis type 2 (NF2).[7,8] About 10% of MPMs are associated with a genetic predisposition, with familial *BAP1* loss mutation being the most common.[9,10]

Since the approval of pemetrexed and platinum-based chemotherapy as the first-line treatment for advanced MPM more than 20 years ago, no significant advances had been made in the treatment of mesothelioma prior to immune checkpoint inhibitor (ICI) therapy; the 5-year survival

rate unfortunately remains below 10%.[11] In the last decade, ICIs have yielded promising results in the treatment of MPM.[12]

In this article, we discuss the clinical trials that examined the addition of immunotherapy in first-line settings (see the section on 'Randomized immunotherapy trials of mesothelioma'). We also discuss the biomarkers of response to ICIs and future directions (see the sections on 'Predictors of response to immune checkpoint inhibitors' and 'Future directions'). Over the past 20 years, a significant amount of clinical and basic research has been conducted to better understand the immunology of mesothelioma.[13–16] However, such a comprehensive article is beyond the scope of this minireview.

Systemic treatment and immunotherapy debut

In 2003, the EMPHACIS (Evaluation of Mesothelioma in a Phase III Trial of Pemetrexed with Cisplatin) study established palliative treatment with pemetrexed and platinum-based doublets as the most active first-line therapy for advanced MPM based on overall survival (OS) benefit and superior quality of life.[11] Further studies showed no role for maintenance pemetrexed after frontline therapy, and outcomes based on histological subtype were not reported.[17]

Recently, the introduction of ICIs has changed the treatment landscape of advanced malignancies. The first study to test immunotherapy in mesothelioma was with avelumab (programmed death-ligand 1 [PD-L1] inhibitor) ICI after disease progression on platinum-based chemotherapy.[13] Only 9% of patients responded, but these responders had durable remission (median 15.2 months), and the disease control rate was 58%. This study triggered greater interest in immunotherapy for mesothelioma. The CONFIRM (CheckpOiNt Blockade For Inhibition of Relapsed Mesothelioma; ClinicalTrials.gov identifier: NCT03063450) phase III study led to a National Comprehensive Cancer Network recommendation for the use of ICIs in second-line settings for mesothelioma.[18] Nivolumab, a programmed cell death-1 (PD-1) inhibitor, was compared with placebo in advanced relapsed MPM in a blinded, randomized clinical trial and showed an OS benefit of 10.2 versus 6.9 months (p<0.01).[19–21] In addition, the phase II multicentre randomized MAPS2 trial (A Randomized Phase II Study Evaluating Efficacy and Safety of Second- or Third-line Treatment by Nivolumab Monotherapy or Nivolumab Plus Ipilimumab, for Unresectable Malignant Pleural Mesothelioma [MPM] Patients; ClinicalTrials.gov identifier: NCT02716272) investigated single-agent nivolumab or its combination with ipilimumab (cytotoxic T-lymphocyte associated protein 4[CTLA-4] inhibitor) and showed a 12-week disease control of 44% (24/54; 95% confidence interval [CI]: 31–58) in the nivolumab group and 50% (27/54; 95% CI: 37–63) in the ipilimumab/nivolumab combination group, showing an added benefit for the ICI combination.[22]

Randomized immunotherapy trials of mesothelioma

This promising clinical efficacy in relapsed pleural mesothelioma supported the need to study ICIs in larger confirmatory clinical trials.

Checkmate 743

Checkmate 743 (A Phase III, Randomized, Open Label Trial of Nivolumab in Combination with Ipilimumab Versus Pemetrexed with Cisplatin or Carboplatin as First-line Therapy in Unresectable Pleural Mesothelioma; ClinicalTrials.gov identifier: NCT02899299) is a phase III clinical trial that investigated the combination of nivolumab and ipilimumab against standard systemic pemetrexed and platinum-based chemotherapy in treatment-naive patients with advanced MPM.[12] Patients with MPM were enrolled regardless of PD-L1 expression and stratified by histology. The immunotherapy-treated patients showed an OS benefit (18.1 versus 14.1 months; hazard ratio [HR] 0.74, p<0.01), leading the US Food and Drug Administration (FDA) to approve immunotherapy as a first-line treatment for mesothelioma.[23] Similar to other ICI trials, the survival curves crossed at around 6 months, regardless of the histological subtype, reflecting an early but not sustained benefit of chemotherapy. Historically, patients with the non-epithelioid subtype had worse clinical outcomes with chemotherapy. However, in patients treated with dual ICIs, clinical efficacy was higher in those with non-epithelioid histologies (median OS 18.1 months; HR 0.46, 95% CI: 0.31–0.68) than in those with the epithelioid histology subtype (median OS 18.7 months; HR 0.86, 95% CI: 0.69–1.08), suggesting an added benefit for the ICI combination in these subtypes. Furthermore, 97% of patients had quantifiable PD-L1 expression at baseline and 77% had PD-L1-positive (≥1%) tumours. Clinical benefit was observed across subgroups, regardless of PD-L1 expression. In the exploratory biomarker analyses, a four-gene inflammatory signature (measuring the expression of *CD8A*, *STAT1*, *LAG3* and *CD274*) score appeared to correlate with OS in patients treated with nivolumab plus ipilimumab (median OS 21.8 versus 16.8 months for high versus low score, respectively), but not in patients receiving chemotherapy. Around 20% of patients in the chemotherapy-only arm received ICIs upon progression, but their survival was worse. The efficacy of the dual-ICI combination in the first-line setting is durable, with a 3-year OS rate of 23 versus 15% for the systemic chemotherapy arm.[24] The frequency of severe treatment-related toxicity (grade ≥3) was similar between the dual-ICI arm (30%) and the systemic chemotherapy arm (32%), with the toxicity profile of dual ICI similar to previous reports.

IND.227/Keynote 483

The IND.227 (Pembrolizumab in Patients with Advanced Malignant Pleural Mesothelioma; ClinicalTrials.gov identifier: NCT02784171) phase II study compared progression-free survival (PFS) of standard platinum and pemetrexed (chemotherapy) versus chemotherapy plus pembrolizumab versus pembrolizumab alone.[25] Patients with untreated advanced pleural mesothelioma were randomized to six cycles of chemotherapy with or without pembrolizumab (an ICI). The pembrolizumab single-agent arm was discontinued early for futility. The primary endpoint was PFS. Although there was no statistically significant difference in PFS between chemotherapy (median PFS of 6.7 months) and chemotherapy plus pembrolizumab (median PFS of 6.8 months), with a stratified HR of 0.55 (95% CI: 0.38–1.06), the chemotherapy plus pembrolizumab arm showed an OS improvement of 19.8 months compared with 8.9 months for chemotherapy alone. Interestingly, the addition of chemotherapy to pembrolizumab yielded a comparable OS benefit to the 17.5-month survival observed in the pembrolizumab-alone arm, suggesting an added benefit of the ICI. The HRs were 0.36 for chemotherapy plus pembrolizumab versus chemotherapy (95% CI: 0.18–0.72) and 0.54 for pembrolizumab alone versus chemotherapy (95% CI: 0.29–1.02) (p=0.08 for the stratified log-rank test). These promising results supported the expansion of the study to a phase III trial comparing chemotherapy with chemotherapy plus pembrolizumab; the primary endpoint was amended to OS.[25]

The final results of the Keynote 483 phase III study on the combination of chemotherapy and immunotherapy for MPM were presented at the American Society of Clinical Oncology 2023 annual meeting.[26,27] The study, which included a total of 440 patients (including 80 from the phase II study), randomized patients 1:1 to platinum-based chemotherapy with or without pembrolizumab. It was a multinational collaboration between the Canadian Cancer Trials Group, the National Cancer Institute of Naples and the French Cooperative Thoracic Intergroup. The OS, the primary

endpoint, was 17.3 months in the pembrolizumab plus chemotherapy arm compared with 16.1 months in the chemotherapy arm (HR 0.79, 95% CI: 0.64–0.98, p=0.0324), with no early crossing of the survival curves. The addition of pembrolizumab to platinum-based chemotherapy in advanced MPM reduced the risk of death by 21% with a higher objective response rate (ORR) of 62% compared with 38% in the chemotherapy-only arm (odds ratio 2.7, 95% CI: 1.8–4.0, p<0.0001). Similar to the Checkmate 743 trial, patients with non-epithelioid histology who received combination treatment with pembrolizumab had a higher magnitude of clinical benefit (median OS of 12.3 months in the pembrolizumab arm versus 8.2 months in the chemotherapy-only arm; HR 0.57, 95% CI: 0.36–0.89) than those with the epithelioid histology subtype (median OS of 19.8 months in the pembrolizumab arm versus 18.2 months in the chemotherapy-only arm; HR 0.89, 95% CI: 0.7–1.13). The addition of ICI to chemotherapy had a durable 2- and 3-year OS benefit of 39 versus 33%, and 25 versus 17%, respectively. Despite a high rate of patients in the chemotherapy-only arm receiving ICI upon progression (28%), their OS was inferior. The significant number of patients receiving ICI in the non-intervention arm upon progression in both the Checkmate 743 and Keynote 483 studies may explain why the chemotherapy arm performed better than historical cohorts.[11] The frequency of severe treatment-related toxicity (grade ≥3) was higher in the pembrolizumab plus chemotherapy arm (27%) compared with the systemic chemotherapy-only arm (15%), with the toxicity profile and rate of ICI and chemotherapy similar to the previous combination trials in non-small-cell lung cancer, including myelosuppression, febrile neutropaenia, diarrhoea and colitis.[28] However, the rate of adverse events leading to the discontinuation of one or more drugs in the pembrolizumab plus chemotherapy arm (37%) was similar to the Checkmate 743 dual-ICI combination arm, with only 16% considered related to pembrolizumab. In September 2024, the FDA granted approval for pembrolizumab in combination with pemetrexed and platinum-based chemotherapy as the first-line treatment of advanced or unresectable MPM.[29]

Predictors of response to immune checkpoint inhibitors

Potential biomarkers of response to ICIs could guide patient selection and treatment optimization. One such study has done extensive translational research, the phase II study of durvalumab (MEDI4736) in combination with chemotherapy for first-line treatment of unresectable mesothelioma (PrE0505; Open Label, Phase II Study of Anti-programmed Death-ligand 1 Antibody, Durvalumab [MEDI4736] in Combination with Chemotherapy for the First-line Treatment of Unresectable Mesothelioma; ClinicalTrials.gov identifier: NCT02899195).[30] However, none of the potential markers have been validated in randomized studies. Hence, currently, there are no predictive biomarkers for identifying patients with mesothelioma who could benefit from immunotherapy treatment. Although outside the scope of this article, other potential biomarkers may be discovered through ongoing research, either specifically for mesothelioma or for other cancers that could be extended to mesothelioma. Tumour microenvironment (TME) and metabolism are being researched with some features that might be important for mesothelioma prognosis.[31,32] Specific to immunotherapy, preliminary studies show that the tumour mutational burden in MPM is relatively low.[33,34] PD-L1 tumour cell expression varies widely between 20 and 70% based on the cut-off value (1 versus 5%) and PD-L1 immunohistochemistry assay used.[35–38] Patients with the non-epithelioid subtype exhibit higher PD-L1 expression and shorter survival than those with the epithelioid subtype.[37–40] In the Checkmate 743 and Keynote 483 phase III studies, over 74 and 60% of patients, respectively, had positive PD-L1 tumour cell expression (≥1%). However, PD-L1-positive expression did not significantly impact the survival benefit associated with ICI, suggesting that PD-L1 expression ≥1% is not a predictive biomarker for ICI benefit. Both studies confirmed the pronounced benefit of ICI in patients with non-epithelioid histology compared with chemotherapy alone. Interestingly, patients have better outcomes when immunotherapy is given as first-line treatment, a finding also seen in many other cancers, including melanoma.[41] An exploratory analysis of the Checkmate 743 data evaluated the inflammatory gene signature (*CD274*, *CD8A*, *LAG3* and *STAT1*) of the TME via RNA sequencing of the baseline samples. A high expression score of the four genes correlated with an improved survival benefit with dual-ICI treatment (HR for OS 0.57, 95% CI: 0.40–0.82) but not with chemotherapy (HR for OS 1.14, 95% CI: 0.82–1.59). MPM is a heterogeneous cancer with a diverse immune landscape beyond PD-L1 and histological subtypes. Further prospective studies are needed to classify and validate gene signatures that may correlate with ICI response and inform therapeutic vulnerabilities.[34,42,43]

For an extensive review of biomarkers in patients with mesothelioma treated with immunotherapy, we refer the reader to the translational studies conducted on patients enrolled in the phase II study of durvalumab with chemotherapy, PrE0505.[44] Integrated genomic and immune cell repertoire analyses were performed in these patients. Results show that a higher immunogenic mutation burden, along with a more diverse T-cell repertoire, is linked to favourable clinical outcomes. A higher degree of genomic instability renders epithelioid mesothelioma more susceptible to immunotherapy. Similarly, germline alterations in cancer-predisposing genes, especially those involved in DNA repair, also increase immunotherapy susceptibility and long-term survival.

Finally, immune-related adverse events (irAEs) have emerged as a potential clinical biomarker for ICI response across multiple malignancies, correlating with improved clinical outcomes in patients who develop irAE toxicity.[45–49] In a subgroup analysis of Checkmate 743 data, patients who received ipilimumab and nivolumab and experienced treatment-related adverse events leading to discontinuation had a higher 3-year OS rate of 37% compared with 23% in all randomized patients.[50] Similar observations were seen in case reports and retrospective studies; however, larger and prospective studies are encouraged to understand the role of irAEs on ICI efficacy in MPM.[51,52]

Future directions

Potential future directions to better use immunotherapy to help improve survival in mesothelioma are reviewed below.

Immunotherapy with chemotherapy

Other planned immunotherapy trials include the DuRvalumab With chEmotherapy as First Line treAtment in Advanced Pleural Mesothelioma (DREAM3R; DREAM3R: DuRvalumab [MEDI4736] With chEmotherapy as First Line treAtment in Advanced Pleural Mesothelioma – A Phase 3 Randomised Trial; ClinicalTrials.gov identifier: NCT04334759), which tests durvalumab with platinum and pemetrexed chemotherapy for four to six cycles, followed by maintenance durvalumab therapy until disease progression, as first-line treatment in advanced pleural mesothelioma in a phase III randomized trial (with a 2:1 randomization).[53] This trial is based on two phase II trials (DREAM and PrE0505) combining the PD-L1 inhibitor durvalumab with standard first-line chemotherapy. Both trials exceeded pre-specified efficacy criteria. Patients enrolled in phase III will be stratified by age (18–70 versus >70 years), sex, histology (epithelioid versus non-epithelioid), planned platinum (cisplatin versus carboplatin) and geographic region (North America versus Oceania). The primary endpoint is OS.

Anti-angiogenesis

Angiogenesis plays a key role in the pathogenesis of MPM. Vascular endothelial growth factor receptor (VEGFR) is notably highly expressed in MPM tumour cells and correlates with poor prognosis.[14,54] Monotherapy studies of vascular endothelial growth factor (VEGF) inhibition were not successful.[55–57] Recent studies in untreated and pretreated patients with MPM with the combination of chemotherapy and VEGFR tyrosine kinase inhibitors or monoclonal antibodies against VEGF showed a small but significant OS benefit.[58,59] Inhibition of VEGFR can enhance ICI efficacy by modifying the immunosuppressive TME and increasing effector T-cell infiltration. This hypothesis led to a study of bevacizumab (an angiogenesis inhibitor) and atezolizumab (an ICI) in patients with peritoneal mesothelioma that resulted in an ORR of 40%, regardless of PD-L1 status, and a median duration of response of 12.8 months.[60] These encouraging findings suggest that the combination of anti-VEGFR and ICI may be effective in advanced MPM and is currently being tested in the BEAT-meso: Bevacizumab and Atezolizumab in Malignant Pleural Mesothelioma (A Multicentre Randomised Phase III Trial Comparing Atezolizumab Plus Bevacizumab and Standard Chemotherapy Versus Bevacizumab and Standard Chemotherapy as First-line Treatment for Advanced Malignant Pleural Mesothelioma; ClinicalTrials.gov identifier: NCT03762018), adding atezolizumab to platinum-based chemotherapy and bevacizumab in the first-line setting for patients with MPM.[61] Final results are currently pending. In addition, Mesothelioma Stratified Therapy, an ongoing phase II multi-arm rolling study, is currently testing the combination of atezolizumab and bevacizumab, as well as other arms based on molecular alteration, such as rucaparib (a poly ADP-ribose polymerase [PARP] inhibitor) and abemaciclib (cyclin-dependent kinases 4/6 [CDK4/6] inhibitor).

Targeted therapies

There is a growing understanding of the molecular heterogeneity and landscape of MPM that may inform therapeutic vulnerabilities.[34,62,63] For example, non-epithelioid MPM is enriched with an argininosuccinate synthase 1 enzyme deficiency, leading to a dependency on exogenous arginine for survival. Pegylated arginine deaminase (ADI-PEG20), which causes arginine deprivation, has shown promising results as a single agent and in combination with chemotherapy, with no additional toxicity. ADI-PEG20 Targeting of Malignancies Induces Cytotoxicity-mesothelioma, known as ATOMIC-meso (A Randomized, Double-blind, Phase 2/3 Study in Subjects with Malignant Pleural Mesothelioma to Assess ADI-PEG 20 with Pemetrexed and Cisplatin [ATOMIC-Meso Phase 2/3 Study]; ClinicalTrials.gov identifier: NCT02709512), is a phase II/III trial currently investigating the combination of ADI-PEG20 with platinum-based chemotherapy in non-epithelioid MPM.[64] YAP1 is highly activated in mesothelioma and there is an ongoing phase I study with VT3989 (Yes-associated protein [YAP]-TEA domain [TEAD] inhibitor) in patients with MPM and other solid malignancies with and without NF2 mutations (NCT04665206).[65] Results from dose escalation phase I study showed promising tolerability and durability of antitumour responses in patients with advanced malignant mesothelioma. The study is still ongoing to identify the recommended phase II dose and dose expansion.

BAP1 is another target that is mutated in more than 50% of MPM cases. *BAP1* mutation may lead to a deficiency in the homologous recombinant pathway, increasing dependency on other DNA-repair pathways.[34] Preclinical studies have shown that *BAP1* loss enhances the expression of EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit), an epigenetic regulator.[66] Targeting *BAP1*-mutant MPM based on therapeutic vulnerabilities with tazemetostat (an EZH2 inhibitor) and rucaparib (a BRCA1 inhibitor) has shown promising results in small phase II studies.[67,68]

These studies are important and may prove to be a promising avenue for effectively treating MPM and developing new therapies based on molecular biomarkers, rather than relying on empiric combinations in unselected patients. Other targets could also support combination treatments with immunotherapy, such as the antibody–drug conjugates (ADCs) and chimeric antigen receptor (CAR)-T cell described below.

Antibody–drug conjugates

ADCs may also be interesting targets against mesothelioma. ADCs are composed of a monoclonal antibody, a chemical linker and a cytotoxic drug. The antibody binds to a target antigen on the tumour cell, causing the ADC to be internalized into the cell. The linker is then cleaved, releasing the drug into the cytoplasm to kill the tumour cell. A few targets are being considered. Trophoblast glycoprotein (*5T4*) is an oncofoetal protein that is overexpressed in mesothelioma, which makes it a good candidate for ADC treatment and other directed therapies, such as SYD1875 ADC conjugated to a duocarmycin-based linker drug (A First-in-human Dose-escalation and Expansion Study with the Antibody-drug Conjugate SYD1875 to Evaluate the Safety, Pharmacokinetics and Efficacy in Patients with 5T4-expressing Locally Advanced or Metastatic Solid Tumours; ClinicalTrials.gov identifier: NCT04202705, ongoing).[69,70] Mesothelin has been targeted many times in mesothelioma.[71] BMS-986148 is a new mesothelin-directed ADC that contains a fully human immunoglobulin G1 anti-mesothelin mAb conjugated to tubulysin, a cytotoxic compound that disrupts the microtubule assembly via a valine–citrulline linker, with an average drug-to-antibody ratio of 3 (not yet in trials). Epidermal growth factor receptor (EGFR) is frequently overexpressed in patients with mesothelioma. ABT-806, a humanized form of the monoclonal antibody 806 (mAb806), is an attractive therapeutic strategy for use as an ADC in tumors that overexpress EGFR.[72] Various payloads are being tested with this antibody. Finally, sacituzumab govitecan, a drug that is FDA-approved for breast and urothelial cancers, targets trophoblast cell-surface antigen 2 (TROP2)-positive cells with SN38, a potent topoisomerase I inhibitor of SN38. TROP-2 is highly expressed in mesothelioma, and currently a phase II study is ongoing investigating the efficacy and safety of sacituzumab govitecan in relapsed mesothelioma (Phase 2 Study of Sacituzumab Govitecan-hziy in Patients with Previously Treated Mesothelioma; ClinicalTrials.gov identifier: NCT06477419).[73]

Chimeric antigen receptor-T cell therapies

Most studies of CAR-T cells for mesothelioma target mesothelin.[74] Mesothelin is highly expressed on the surface of about 30% of cancers, including mesothelioma. Mesothelin also sheds after being cleaved by proteases, leaving a short peptide attached to the cell. Most anti-mesothelin antibodies bind to shed mesothelin, which can prevent their binding to target cells. Newer antibodies bind next to the membrane at the protease-sensitive region to make CAR-T cells that have much higher anti-tumour activity. One example is the highly active h15B6 CAR-T.

Conclusion

MPM is a heterogeneous disease with multiple histological subtypes and an evolving understanding of its molecular landscape and TME characteristics. The Checkmate 743 and Keynote 483 studies established immunotherapy as a first-line treatment for patients with advanced MPM with non-epithelioid subtype showing superior clinical benefit to ICI than to chemotherapy. Beyond histology, the clinical benefit of ICIs in MPM is currently biomarker agnostic, and prospective studies are needed to identify predictive biomarkers. The field is moving towards biological

targets instead of empiric combinations to better select patients and draft rational designs of innovative therapeutic combinations for MPM based on therapeutic vulnerabilities. ❑

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