

REVIEW ARTICLE

Systemic Treatments for Unresectable Pleural Mesothelioma: A Review of the Literature

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ABSTRACT

Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer with a poor prognosis. Most patients have unresectable disease at the time of diagnosis, for which palliative chemotherapy has been the standard of care for years. Despite the effort to improve systemic treatment, the prognosis remains poor, with a median overall survival of about 17–18 months. Recently, in the CheckMate 743 trial, the combination of nivolumab and ipilimumab showed improved overall survival compared with standard chemotherapy. After years, this study has challenged the role of chemotherapy as a standard of care and positioned the chemotherapy-sparing regimen as a valid alternative in the first-line MPM setting. Several new therapies other than immune checkpoint inhibitors are under consideration and might have an impact on standard practice in the near future. This review aims to revisit the systemic treatments currently recommended and those under study, as well as to explore future perspectives.

Keywords: Malignant pleural mesothelioma, immunotherapy, immune checkpoint inhibitors, targeted therapy

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an incurable cancer of the pleural surface. Its incidence has been rising in Europe, and the peak is expected between 2021–2025. The most important and known risk factor is the inhalation of asbestos fibers in 80% of cases.¹ Some studies have recently pointed out that a germline mutation in the *BAP1* (BRCA1 associated protein 1) gene might be implicated in the predisposition to MPM.² Although asbestos is banned in many countries, developing countries continue to use it, and the incidence of MPM remains increasing because of the latency period between exposure to asbestos and the onset of cancer.^{3,4} MPM is divided into three histological subtypes: the most prevalent epithelioid, sarcomatoid with the poorest prognosis, and the biphasic. Diagnosis is often tardive due to unspecific symptoms such as shortness of breath, chest pain, and weight loss. Until recently, the first-line treatment included chemotherapy with or without an anti-angiogenic monoclonal antibody drug, bevacizumab. Currently, there is no real standard for second and later lines. No actionable driver mutations have been identified in MPM to date. Moreover, MPM carcinogenesis is influenced by many factors such as BRCA-associated protein 1 (BAP1), overexpression of growth factors such as vascular endothelial growth factor (VEGF), CDKN2A and neurofibromatosis type 2 (NF2) tumor suppressor inactivation, mesothelin (MSLN) promoter methylation, and Ras/mitogen-activated protein kinase and phosphatidylinositol 3-kinase/mTOR pathway activation.^{5,6}

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FIRST-LINE THERAPY

CHEMOTHERAPY

The most prevalent first-line therapy for unresectable MPM is a combination doublet of cisplatin with pemetrexed. This treatment regimen was studied in a phase III trial, which randomized 456 patients to receive cisplatin 75 mg/m² alone or in combination with pemetrexed 500 mg/m² every 3 weeks, with overall survival (OS) as the primary outcome.⁷ All patients also received 350–1,000 µg of folic acid daily for 1–3 weeks before the first chemotherapy and thereafter throughout the study. Furthermore, 1,000 µg of vitamin B12 was given 1–3 weeks before the first treatment and then every 9 weeks. The results showed a longer median OS in the pemetrexed/cisplatin arm (12.1 months vs 9.3 months with cisplatin; $p=0.020$), with a response rate of 40%. Instead of pemetrexed, raltitrexed, a thymidine synthase inhibitor, was studied with cisplatin in a randomized phase III study. A total of 250 patients received either cisplatin alone (80 mg/m² i.v. on day 1 and every 3 weeks) or in combination with raltitrexed (3 mg/m² i.v. every 3 weeks). The primary outcome was OS. The objective response rate (ORR) was 14% in the cisplatin arm and 24% in the combination arm, with a median OS of 8.8 months (95% CI: 7.8–10.8) and 11.4 months (95% CI: 10.1–15), respectively.⁸

For elderly patients, carboplatin can be an alternative to cisplatin^{9,10} due to its lower renal toxicity. The doublet cisplatin and gemcitabine has also been studied in a phase II trial and might be an important treatment regimen for patients who do not tolerate pemetrexed or raltitrexed.¹¹

ANTI-ANGIOGENIC AGENTS

Anti-angiogenic agents have been assessed in combination with chemotherapy. In the French phase III MAPS trial, the addition of bevacizumab to first-line platinum doublet led to improved progression-free survival (PFS) (9.2 months vs 7.3 months with platinum doublet alone) and OS (18.8 months vs 16.1 months; $p=0.0167$)¹², with a manageable toxicity profile. Despite the positive result, this regimen has not been widely adopted due to the lack of formal Food and Drug Administration (FDA) or European Medicines Agency (EMA) approval for the bevacizumab in this indication. Tyrosine kinase inhibitors (TKIs) have also been explored, and the phase II LUME-Meso trial showed an improvement in the median PFS with nintedanib plus chemotherapy versus chemotherapy alone (9.7 months vs 4.7 months).¹³ The findings were not yet confirmed in a larger phase III trial.¹⁴ Similarly, the addition of another TKI, axitinib, to chemotherapy has not shown any improvement in neither PFS nor OS.¹⁵

IMMUNOTHERAPY

Immune checkpoint inhibitors (ICI) have revolutionized the treatment of many cancers. Recently, the randomized phase III CheckMate 743 trial compared the combination of nivolumab

and ipilimumab with platinum doublet chemotherapy in the first-line setting. The primary endpoint of the study were OS and PFS. The median OS was significantly improved in the nivolumab/ipilimumab arm as compared with the chemotherapy arm (18.1 months vs 14.1 months; $p=0.002$). In epithelioid histologies, which represents 75% of cases in this study, a trend for OS benefit was observed but statistical significance was not reached (median OS: 18.7 months vs 16.5 months; HR: 0.69 [95% CI: 0.69–1.08]), while non-epithelioid histologies were associated with significantly prolonged median OS (18.1 months vs 8.8 months; HR: 0.69 [95% CI: 0.31–0.68]). The median PFS was similar in both arms. Further analysis showed comparable median OS among patients with a programmed death-ligand 1 (PD-L1) expression of less than 1% in the two study arms. Conversely, in patients with PD-L1 expression of 1% or higher, the treatment of nivolumab plus ipilimumab showed a better median OS, as compared with chemotherapy (18.0 months vs 13.3 months; HR: 0.69). Regarding safety, grade 3–4 adverse events occurred in 30.3% of patients on nivolumab plus ipilimumab (discontinuation rate: 15%) and 32% of patients on chemotherapy (discontinuation rate: 7.4%).¹⁶ This is the first phase III study showing a significant improvement in OS with immunotherapy compared to standard chemotherapy, thus offering a new first-line option. Epithelioid and non-epithelioid histologies both appear to benefit from dual immunotherapy, although OS benefit was more evident in the sarcomatoid group. Similarly, OS benefit was seen in both groups, PD-L1 > or < 1%, although data should be interpreted with caution as descriptive in nature and PD-L1 should not be considered as a biomarker as such for mesothelioma, based on these results, the FDA approved the combination of nivolumab plus ipilimumab as a first-line treatment in October 2020.

Due to the proven efficacy of bevacizumab in combination with first-line chemotherapy, the ongoing randomized, phase III BEAT-meso trial is exploring atezolizumab plus bevacizumab with standard chemotherapy versus bevacizumab and chemotherapy. There are two co-primary outcomes, OS and PFS. This study is currently completing accrual.

NOVOTTF-100L

The NovoTTF-100L system is a portable battery that sends very low intensity alternating electric fields to the tumor site, called tumor treatment fields (TTFields) within the human body. The treatment goal is to slow down the tumor cell replication and thus inhibit tumor growth.¹⁷ In phase II STELLAR trial, 80 patients were treated with a combination of continuous 150 kHz Fields (>18 hours/day) and chemotherapy (pemetrexed and cisplatin or carboplatin). The primary endpoint of the study was OS. After a minimum follow-up of 12 months, the median OS was 18.2 months (95% CI: 12.1–25.8) compared with 12.1 months in the historical control, with a low toxicity profile.¹⁸ Based on these results, the FDA approved this treatment regimen in 2019.

MAINTENANCE

So far, a few studies have evaluated maintenance therapy with mixed results. A phase II trial from the Cancer and Leukemia Group B (CALGB) assessed pemetrexed maintenance versus observation after 4–6 cycles of doublet chemotherapy. The trial did not show prolonged median PFS compared with placebo (3.4 months vs 3.0 months; $p=0.9733$).¹⁹ The results of the COMMAND trial, which investigated defactinib maintenance in 344 MPM patients, were also negative for PFS and OS.²⁰ Only the phase II NVALT19 study evaluating gemcitabine maintenance versus best supportive care showed a significantly longer median PFS in the gemcitabine arm (6.2 months vs 3.2 months; $p<0.0001$).²¹

SECOND-LINE AND BEYOND

CHEMOTHERAPY

For patients with disease progression after first-line chemotherapy, there is currently no standard therapy. Retreatment with pemetrexed with or without a platinum agent can be proposed for a patient with PFS of more than 3 months after first-line pemetrexed-based chemotherapy (PBC). The benefit is greater in case of PFS >12 months (PFS after re-treatment: 5.5 months vs 2.5 months if initial PFS <12 months).²² In a phase II trial, weekly vinorelbine (30 mg/m²) showed a response rate of 16% and a median OS of 9.6 months.²³ However, no phase III studies have confirmed these data.

IMMUNOTHERAPY

The efficacy of anti-programmed cell death 1 (PD-1), nivolumab and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), ipilimumab was studied in the phase II, multicenter, randomized MAPS2 trial in patients who had progressed after receiving 1 or 2 prior lines of treatment, including platinum-containing therapy. Overall, 108 patients were randomized 1:1 to receive either nivolumab (3 mg/kg every 2 weeks), or nivolumab plus ipilimumab (1 mg/kg every 6 weeks), until disease progression or unacceptable toxicity. The primary endpoint was the proportion of patients who achieved 12-week disease control, which was 44% in the nivolumab group (24/54 patients) and 50% (27/54 patients) in the nivolumab plus ipilimumab group.²⁴ The recently randomized, phase III, double-blind CONFIRM trial studied nivolumab versus placebo after at least 1 prior line of therapy (including re-challenge with platinum/pemetrexed), which must be completed at least 14 days before the treatment. Patients were randomized 2:1 to receive

either nivolumab alone or placebo. The co-primary endpoints are OS and PFS, and the secondary endpoint is OS according to PD-L1 status, ORR and toxicity, among others. OS and PFS were significantly improved in the experimental arm with HR 0.72 (OS: 9.2 months vs 6.6 months respectively; $p=0.02$; PFS: 3.0 months vs 1.8 months; $p<0.001$). There was no statistically significant association between survival and PD-L1 status.²⁵ To prove, once more the importance of biomarker-based treatment selection, the randomized, phase III PROMISE-meso trial evaluated pembrolizumab versus standard chemotherapy in MPM patients. Patients were randomized (1:1) into two arms: one received pembrolizumab (200 mg i.v. every 3 weeks), and the other received either gemcitabine (1,000 mg/m²) every 3 weeks or vinorelbine (30 mg/m² i.v. or 60–80 mg/m² orally), on days 1 and 8, every 3 weeks, until disease progression or for up to 2 years for pembrolizumab. The primary endpoint was PFS. The median PFS was 2.5 months for the pembrolizumab versus 3.4 months in the chemotherapy arm. Of note, ORR was 22% for the pembrolizumab arm versus 6% in the chemotherapy arm ($p=0.004$), but no significant difference in OS was observed.²⁶

FUTURE THERAPY OR PROSPECTIVE

CAR T-CELL THERAPY

The chimeric antigen receptor (CAR) T cells have shown particularly good results in the treatment of hematological malignancies, especially in acute lymphoblastic leukemia (ALL) and B lymphomas.

Given these positive results, studies have been conducted on solid tumors, and recently, the results of a first phase I study on MPM were reported. The study investigated the fibroblast activating protein (FAP) targeting CART-cells (CART-FAP) to determine the toxicity and feasibility of the treatment. In total, 4 patients were included in the trial, but only 3 received CAR T cells. All patients had metastatic unresectable MPM and received 3 cycles of chemotherapy before injecting 1×10^6 CART-FAP, which is the lowest recommended dose for the second generation of CAR T-cells (with CD-28 signaling domain) because FAP was for the first time examined as a target. One of the patients had a systemic expansion of CART-FAP cells in the blood, showing that local administration can lead to systemic distribution. Elevated concentrations of proinflammatory cytokines suggest an ongoing immune response. No grade 4 adverse events were reported. Future clinical trials are ongoing to further explore the efficacy of CAR T-cell therapies in MPM.²⁷

ANTI-MESOTHELIN

The mesothelin (MSLN) is a glycoprotein expressed on the surface of mesothelial cells.^{28,29} MSLN overexpression in MPM seems to have a role in tumor growth and invasion³⁰, making MSLN a possible therapeutic target. A phase II (NCT00738582) study assessed the combination of amatuximab, a chimeric monoclonal antibody to mesothelin, with chemotherapy (pemetrexed and cisplatin), which showed a median OS of 14.8 months (95% CI: 12.4–18.5).³¹ The ARTEMIS trial (NCT02357147), a phase II study assessing amatuximab, was closed prematurely for financial considerations. A phase I study (NCT01675765) assessed the sequential administration of cancer vaccine CRS-207, a genetically modified listeria monocytogenes, with or without cyclophosphamide, followed by pemetrexed and cisplatin. The study recruited 35 patients, of which 89% had disease control with one complete response; 54% of the patients achieved a partial response and 29% stable disease. The median OS was 14.7 months (95% CI: 11.2–21.9).³²

The LMB-100 is a recombinant immunotoxin composed of an antibody directed against mesothelin and a fragment of *Pseudomonas* exotoxin A. A phase I (NCT02798536) assessed the safety dose and anti-tumor activity of LMB-100 for patients with advanced pleural mesothelioma that have progressed after first-line platinum-based chemotherapy.³³ An ongoing phase I/II (NCT03126630) is assessing pembrolizumab with or without anetumab ravtansine, an anti-MSLN antibody conjugated with the cytotoxic anti-tubulin drug ravtansine.

SYNTHETIC LETHAL THERAPIES

Loss of expression of the arginine-succinate synthetase 1 (ASS1) gene was demonstrated in some MPM, mostly in the biphasic and sarcomatoid histologies, with an inability to synthesize ASS1. ASS1 is a rate-limiting enzyme in the production of arginine, a precursor of molecules that are important in tumorigenesis. The results of the phase I TRAP trial (NCT02029690) showed improved efficacy of pegylated arginine deaminase (ADI-PEG 20), which leads to the depletion of arginine in ASS1-deficient MPM patients.³⁴ To confirm these results, the ongoing phase III ATOMIC-Meso trial (NCT02709512) has been initiated.

BAP1 is a protein involved in different cellular mechanisms such as DNA repair and differentiation. About half of the patients with MPM have inactivating somatic mutations in the *BAP1* gene. As BAP-1 deficiency is linked to increased expression of EZH2 (enhancer of zeste-homolog 2)³⁵, a phase II (NCT02860286) study investigated tazemetostat, an EZH2 inhibitor, in patients with inactive BAP-1 MPM and showed promising anti-tumor activity as monotherapy.³⁶

ONCOVIRAL THERAPY

The phase III INFINITE trial is currently assessing the efficacy of intrapleural administration of adenovirus-delivered interferon alpha-2b in combination with celecoxib and gemcitabine in the second or third-line; the results are expected in 2024. An upcoming phase II trial (NCT04013334) will explore the safety and efficacy of a combination of infusions of nivolumab every 4 weeks and intratumoral injections of MTG201, a replication-incompetent adenovirus into which the gene for REIC/Dkk-3 has been inserted. The trial is going to recruit patients who have progressed on chemotherapy. The intrapleural administration of HSV-1716, an oncolytic virus, was previously assessed in a phase I/IIa, dose-escalation trial (NCT01721018). In total, 12 patients were included, out of whom 3 received 1 dose of intrapleural HSV1716, 3 received 2 doses, and 6 received 4 doses with good tolerance. Anti-tumor immune response was observed with HSV1716 replication and pleural Th1 cytokine responses.³⁷

DENDRITIC CELL VACCINATION

The phase Ib MESOVAX trial (NCT03546426) aimed to explore the efficacy of pembrolizumab plus autologous dendritic cell vaccine in patients with PD-L1 negative expression and advanced mesothelioma after prior therapies. The study will assess the ability to increase the PD-L1 expression on cancer cells. The currently recruiting randomized, phase II/III DENIM trial (NCT03610360) will evaluate the efficacy and anti-tumor activity of dendritic cell immunotherapy with MesoPher plus best supportive care compared with supportive care alone. The primary outcome of this trial is OS.³⁸

MIRNA REPLACEMENT

In many cancers, including MPM, miRNA expression is dysregulated.³⁹ The “miRNA replacement” consists of reintroducing specific miRNAs into tumor cells to compensate for the loss of expression of some miRNA. This could reactivate cellular pathways that lead to therapeutic responses.⁴⁰ A phase I trial (NCT02369198) evaluated TargomiRs, a miRNA mimic delivered by targeted bacterial minicells, with positive results.⁴¹

Table 1. Results of several clinical trials in malignant pleural mesothelioma (MPM). ADI-PEG20, pegylated arginine deiminase; BSC, best supportive care; CT, chemotherapy; DCV, dendritic cell vaccination; DCR, disease control rate; inj, injection; MS: median survival, Neg, negative; NS, not significant; OS, overall survival; Pos, positive; RR, response rate; P-C, pemetrexed-cisplatin; PFS, progression-free survival; rAd-IFN, adenovirus-Delivered Interferon Alpha-2b.

Trial	Phase	Drug	Results	Status
FIRST-LINE THERAPY				
Chemotherapy				
Vogelzang et al. ⁷	III	Cisplatin (C) +/- pemetrexed (P)	MS: 12.1 months with the doublet vs 9.3	Pos
Van Meerbeeck et al. ⁸	III	Cisplatin +/- raltitrexed	OS: 11.4 months with the doublet vs 8.8	Pos
Santoro et al. ⁹	-	Pemetrexed + (cisplatin or carboplatin)	ORR: 26.3% in the pemetrexed + cisplatin group vs 21.7% in the pemetrexed + carboplatin group	Pos
Ceresoli et al. ¹⁰	II	Pemetrexed + carboplatin	RR: 23.8% in the <70 years group vs RR: 14.6% in the >70 years group	Pos
Byrne et al. ¹¹	II	Cisplatin + gemcitabine	RR: 47.6%, PFS: 25 weeks, OS: 41 weeks	Pos
Anti-angiogenic agents				
Zalcman et al. ¹² - MAPS	III	P-C +/- bevacizumab (B)	OS: 18.8 months in the B. group, vs 16.1 months	Pos
Grosso et al. ¹³	II	P-C +/- nintedanib (N)	PFS: 9.7 months in the N. group, vs 5.7 months	Pos
Scagliotti et al. ¹⁴ - LUME-Meso	III	P-C +/- nintedanib	PFS: 6.8 months in the N. group, vs 7.0 months	Neg
Buikhuisen et al. ¹⁵	II	P-C +/- axitinib (A)	NS	Neg
Immunotherapy				
Baas et al. ¹⁶ - CHECKMATE 743	III	CT vs nivolumab (N) + ipilimumab (I)	OS: 18.1 months in the N+I group, vs 14.1 (CT group)	Pos
NCT03762018 - BEAT-meso	III	CT + bevacizumab +/- atezolizumab	-	Recruiting
NovoTTF-100L				
Ceresoli et al. ¹⁸ - STELLAR	II	CT + TTFields	OS: 18.2 months in the TTFields group vs 12.1 months	Pos
MAINTENANCE				
Chemotherapy				
Dudek et al. ¹⁹	II	Pemetrexed vs observation	NS	Neg
Dean A Fennell et al. ²⁰ - COMMAND	II	Defactinib vs placebo	NS	Neg
Burgers et al. ²¹ - NVALT19	II	Gemcitabine (G) vs BSC	PFS: 6.2 months in the G. group vs 3.2 months	Pos
SECOND LINE AND BEYOND				
Chemotherapy				
Ceresoli et al. ²²	-	Retreatment by pemetrexed-based CT	PFS: 3.8 months, OS: 1.5 months	-
Stebbing et al. ²³	II	Weekly vinorelbine	RR: 16%, OS: 9.6 months	Pos
Immunotherapy				
Scherpereel et al. ²⁴ - MAPS2	II	Nivolumab vs nivolumab+ipilimumab (NI)	12-weeks DCR: 50% in the NI group, vs 44%	Pos
Fennell et al. ²⁵ - CONFIRM	III	Nivolumab vs placebo	OS: 9.2 months in the N. group vs 6.6 months	Pos
Popat et al. ²⁶ - PROMISE-Meso	III	Pembrolizumab (P) vs CT single agent	PFS: 2.5 months for P. group, vs 3.4, OS: NS	Neg
FUTURE THERAPY OR PROSPECTIVE				
CAR T cells				
Hiltbrunner et al. ²⁷ - FAPME	I	CART-FAP (fibroblast activating protein)	Safety and persistence of intra-pleural CART-FAP	Pos
Anti-mesothelin				
Hassan et al. ³¹	II	CT + amatuximab	PFS: 6.1 months, OS: 14.8 months	Neg
Hassan et al. ³²	I	Vaccine CRS-2017 +/- cyclophosphamide followed by pemetrexed and cisplatin	Median OS: 14.7 months	Pos
Zhang et al. ³³	I	LMB-100 + nab-paclitaxel	Safety and anti-tumor activity	Pos
NCT03126630	I/II	Pembrolizumab +/- anetumab ravtansine	-	Recruiting
Synthetic lethal therapies				
Beddowes et al. ³⁴ - TRAP	I	CT + ADI-PEG 20	Recommended dose, safety, and tolerability	Pos
NCT02709512 - ATOMIC	II/III	CT +/- ADI-PEG 20 or placebo	-	Recruiting
Zauderer et al. ³⁶	II	Tazemetostat	12-weeks DCR: 47%	Pos
Oncoviral therapy				
NCT03710876 - INFINITE	III	Gemcitabine + celecoxib +/- rAd-IFN	-	Recruiting
NCT04013334	II	Nivolumab + MTG201 intratumoral inj.	-	Recruiting
Danson et al. ³⁷	I/IIa	HSV-1716 intra-pleural delivery	Safety and efficacy	Pos
Dendritic cell vaccination				
NCT03546426 - MESOVAX	Ib	Pembrolizumab + DCV	-	Recruiting
Belderbos et al. ³⁸ - DENIM	II/III	Tumor lysate-pulsed DCV + BSC vs BSC	-	Recruiting
miRNA replacement				
van Zandwijk et al. ⁴¹	I	TargomiRs	Median OS: 200 days (6.7 months), DCR: 73%	Pos

CONCLUSIONS

Over the last years, many clinical trials (Table 1) have contributed to expanding our knowledge about the physiopathology of malignant pleural mesothelioma (MPM). Despite negative data as the second-line therapy in the PROMISE trial, immune checkpoint inhibitors have represented a real step up in the treatment of MPM in the first-line setting and should therefore be considered a valid alternative to doublet platinum-based chemotherapy.

Many questions remain unanswered, in particular about the patient's selection. So far, no valid biomarker has been identified, despite many of them having been investigated.

Given the recent data released, there is a more realistic hope about the treatment for patients with MPM. Further research and studies are warranted to personalized patient treatment as, up to date, and or much work remains to be done to continue this trend and improve the quality of life of our patients with MPM.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

TAKE-HOME MESSAGES

- Immune checkpoint inhibitors (ICI) represent a real step up in the treatment of mesothelioma (MPM) in the first-line setting and therefore should be considered a valid alternative to doublet platinum-based chemotherapy
- Further investigations in this field are necessary for personalized treatment of patients with MPM

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