Review Article

The role of immunotherapy in mesothelioma

Gina Colarusso, Julie Terzic, Vérane Achard, Alex Friedlaender

Department of Oncology, Geneva University Hospital, Geneva, Switzerland

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Correspondence to: Alex Friedlaender. Geneva University Hospital, 4 rue Gabrielle-Perret Gentil, 1205 Geneva, Switzerland.
Email: alex.friedlaender@hcuge.ch.

Abstract: Malignant pleural mesothelioma (MPM) is a rare tumour occurring after asbestos exposure. Most cases are unresectable at the time of diagnosis and the prognosis is very poor. Platinum based chemotherapy, with or without added antiangiogenics is standard first-line treatment. However, its efficacy is limited, patients with unresectable disease have a median 12 months overall survival and the benefit of treatment is only 3 months. The immune micro-environment plays a crucial role in tumour development. Local immunosuppression involving, but not limited to, the expression of T cell inhibitory receptors, favours tumour growth. Moreover, chronic stromal inflammatory response and the presence of lymphocytic infiltration and macrophages are all prognostic factors. Immune checkpoint inhibitors (ICIs) targeting programmed death protein 1 (PD-1), its ligand (PD-L1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) are able to block inhibitory signals on T cells, thus enhancing the immune anti-tumour response. PD-L1 is expressed in 60% of MPM and associated with poor prognosis. Several studies have shown encouraging results in single agent or combination checkpoint inhibition in MPM. Furthermore, T cell-mediated treatments are being developed with promising results, as are chimeric antigen receptor (CAR) T cells targeting mesothelin, a highly expressed protein in MPM. In this review, we examine currently available data, as well as ongoing trials in the field of immuno-oncology for MPM.

Keywords: Mesothelioma; immunotherapy; checkpoint-inhibitors; immuno-oncology; CAR T-cells

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Introduction

Mesothelioma is an insidious neoplasm arising from the mesothelial surfaces of the pleural and peritoneal cavities, the tunica vaginalis or the pericardium. Eighty percent of cases are of pleural origin. The incidence of malignant mesothelioma (MM) differs by gender and region, ranging from ten cases per million people (in the USA) to 29 cases per million people (in Australia and in the UK). It is more common among males (1,2).

The main risk factor for malignant pleural mesothelioma (MPM) is asbestos exposure, responsible for at least 80% of cases (3). In developed countries, the incidence of MPM is expected to peak in next decade, as there is a lag-time of 20–50 years after exposure, and regulation of asbestos was implemented in the 1970s and 1980s. Although smoking and asbestos exposure can multiplicatively increase the risk of developing lung cancer, smoking is not an independent risk factor (4).

Mesothelioma usually presents in the fifth to seventh decades of life. Typical symptoms are chest pain, dyspnea and weight loss (5). Clinically, distinguishing MPM from benign pleural effusions is challenging (6). Imaging investigations in suspected MPM can guide investigations, and the International Mesothelioma Interest Group now advises to diagnose epithelioid mesothelioma with cytological analysis on pleural fluid (7).

Patients with MPM have a very poor prognosis, with

only a modest benefit conferred by modern therapeutics (8). Histological subtype is an important prognostic indicator, with progressively shorter survival in epithelioid MM, biphasic MM, and sarcomatoid MM (9).

A selected minority (<10%) of patients is eligible for a radical multi-modal treatment with a combination of systemic chemotherapy, surgery and/or radiotherapy (RT), in an effort to maintain locoregional tumour control after achieving a macroscopically complete resection. However, as of yet there is no standard of care for this so-called multimodality treatment (10). The 2018 British Thoracic Society (BTS) recommendations advise against extrapleural pneumonectomy in any way and against pleurectomy or decortication outside of clinical trials (11). Based on the results of the MAPS trial, they suggest the association of bevacizumab to a platinum-antifolate doublet to improve survival (12). Most patients have unresectable disease at diagnosis and a 12-month median overall survival with treatment. In these patients, doublet chemotherapies confer a 3-month median survival benefit (10).

Over the past decade, many therapeutic advances have been tested in MPM, including anti-angiogenic treatments and targeted therapies, with limited benefits (12). In this review, we will discuss the role of immunotherapy in MPM.

Methods

For the purpose of this review, we searched the term "pleural mesothelioma" on the publicly available clinical trials database (https://www.clinicaltrials.gov/). This yielded 187 results at the time of our search. We narrowed our focus to trials using immunotherapy. We excluded studies that were non-therapeutic, energy therapy focused (including radiation therapy), systemic chemotherapy focused, kinase inhibitor or other non-antibody inhibitor focused, and those designated as suspended, withdrawn, or with an unknown status.

Ultimately, 21 trials met our criteria; these trials have been categorized into two groups: immune checkpoint inhibitors (ICIs) and non-ICIs.

Furthermore, we performed a literature review on published data.

MPM tumor immune microenvironment

MPM is thought to stem from chronic inflammation following trapped asbestos fibres in the pleura.

A tumour microenvironment study found chronic stromal inflammatory response to be an independent predictor of survival (13). An investigation of immune responses in tumour and tumour-associated stroma in epithelioid MPM showed that high CD163+ tumour-associated macrophages and low CD8+ tumour infiltrating lymphocytes (TILs) were associated with poor prognosis, while low CD163+ tumour-associated macrophages and high CD20+ lymphocyte infiltration conferred an improved prognosis (14). Multiple studies have demonstrated the prognostic role of B cells, T cells and macrophages (14-17). Other investigators have published data showing the presence of immunosuppression in MPM through analysis of T-cell inhibitory receptors (18) and chemokines, such as C-C motif chemokine ligand 2 (CCL2), which is a factor in the protumour M2 macrophage recruitment (19). To tilt the immune microenvironment balance towards an anti-tumour immune response, several immunomodulatory agents are currently being investigated.

ICIs

Under normal circumstances, tumour neoantigens elicit an immune response involving effector T cells and TILs. Tumour cells can adapt through the upregulation of cell surface inhibitory ligands. TILs express inhibitory receptors that bind to these ligands resulting in T-cell apoptosis and immune inhibition. These inhibitory receptors, also known as immune checkpoints, act as a regulatory system that prevent autoimmune reactions, but simultaneously play a crucial role in tumour development. Novel drugs known as ICIs are monoclonal antibodies (mAbs) able to interrupt inhibitory immune signals and to restore anti-tumour immune responses due to their interaction with checkpoint pathways such as cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death protein 1 (PD-1), and its ligand (PD-L1).

Anti CTLA-4

CTLA-4 is a glycoprotein expressed by activated T cells and regulatory T cells (Tregs), where it acts as an inhibitory regulator of the T cell mediated immune response; CTLA-4 competes with the co-stimulatory receptor CD-28 for B7 ligands (CD-80 and CD-86) expressed on antigen presenting cells (APCs). CTLA-4/CD-80 binding results in signalling that directly inhibits T-cell effector function. Consequently, mAbs that block the interaction of CTLA-4 with its ligands can enhance immune response including

anti-tumour immunity. Two anti-CTL4 are currently available, ipilimumab and tremelimumab.

Ipilimumab, an IgG1 monoclonal antibody, was the first ICI to demonstrate a survival benefit. After initial studies in melanoma, it was investigated alone and in combination with PD1 blockade in numerous cancers. In MPM, it has mainly been evaluated in combination with PD1 blockade, and we will discuss its efficacy alongside that of PD1 inhibitors.

Tremelimumab, a selective human IgG2 anti-CTLA-4 monoclonal antibody, showed efficacy in two small phase 2 studies called MESOT-TREM-2008 and MESOT-TREM-2012 and in April 2015, it received orphan drug designation by the US Food and Drug Administration (FDA) to treat MPM (20,21). MESOT-TREM-2008 is a phase 2 study, evaluating tremelimumab in second-line MPM patients. Despite a 7% objective response rate (ORR), the disease control rate (DCR) and 2-year survival rate were 31%, and 36%, respectively (20). These promising results were corroborated in the phase II MESOT-TREM-2012 in 29 additional second-line MPM patients (21). In this second study, tremelimumab was given at an intensified dosing schedule of 10 mg/kg IV every 4 weeks for 6 doses, followed by administration of tremelimumab every 12 weeks, based on previous pharmacokinetic data in metastatic melanoma patients (22). There was a 14% ORR, a 52% DCR with a 10.9-month median duration of response and 11.3-month OS. Grade 3–4 treatment-related toxicity was observed in 7% of patients.

On this basis, Maio *et al.* conducted the DETERMINE trial, a large phase 2b randomized placebo-controlled study of tremelimumab administered in 571 pretreated patients with pleural (95%) or peritoneal mesothelioma with the same treatment schedule as in MESOT-TREM-2012 (23). However, no OS nor DCR benefit was found. Thus, single agent anti-CTLA4 therapy cannot be recommended in MPM.

Anti PD-1

PD-1 is a transmembrane inhibitory immune receptor, expressed on activated T, B, and natural killer cells (24). It binds to PD-L1 or PD-L2 that are expressed on stromal and tumour cells. These interactions lead to T-cell exhaustion, with reduced cytokine release, cellular proliferation, and ultimately cause apoptosis. Blocking PD-1 or PD-L1 by immunomodulating mAb, reinvigorates T cell activation, unleashing an immune response towards the tumour (25). PD-L1 expression is found in up to 60% of MPM samples, with a higher rate in the sarcomatoid histotype, and is associated with poor prognosis. The median overall survival in PD-L1 expressing advanced mesothelioma is 5 months, while it is 14.5 months in PD-L1 negative mesothelioma (26-29).

Nivolumab, a fully humanized anti-PD1 mAb, has been investigated in multiple MPM trials. The NIVOMES trial is a single arm, phase 2 trial in 34 previously treated patients with MPM. Patients received nivolumab 3 mg/kg every two weeks. At three months, there was a 24% ORR and 47% DCR. The results were not correlated to PD-L1 expression. Grade 3–4 adverse events occurred in 26% of patients (30). These results were echoed by the phase 2 MERIT study, investigating nivolumab at a flat dose of 240 mg IV every 2 weeks in 34 second or third line MPM. There was a 29.4% ORR and 67.6% DCR, and the PFS was 6.1 months, while the median OS was not reached at the time of that analysis (31).

The aptly named CONFIRM trial is an ongoing phase 3 double-blind, placebo-controlled study aiming to confirm the benefit of nivolumab in pre-treated mesothelioma patients. In this study, patients who progressed after at least two prior lines of chemotherapy are randomized to nivolumab at a flat dose of 240 mg or placebo. The trial recently opened in the United Kingdom, and will enrol 336 patients (32).

Pembrolizumab is another anti PD-1 mAb that has been investigated in MPM. In the phase 1B multi—cohort Keynote 028 study in pre-treated MPM, pembrolizumab was administered at 10 mg/kg every 2 weeks in 25 MPM patients. 20% achieved a PR, 52% a SD, and the median DOR was 1 year. Interestingly, the median PFS was 5.4 months while the median OS was 18.0 months (33). These encouraging results led to multiple pembrolizumab trials in MPM.

In a phase 2 trial in previously treated pleural or peritoneal mesothelioma, three-weekly 200mg pembrolizumab was administered to 65 mesothelioma patients (86% pleural, 14% peritoneal). In the MPM cohort, the ORR was 20%; interestingly, with a 40% ORR in sarcomatoid subtypes. Median PFS was 4.5 months and OS 11.5 months. Grade 3–5 toxicity occurred in nearly 20% of patients. There was a trend toward higher ORR and PFS with PD-L1 expression (34).

A large multicentre randomized phase 3 ETOP trial, PROMISE-meso, is ongoing. It has included 144 pre-treated MPM patients and is comparing pembrolizumab to standard chemotherapy. Pembrolizumab is administrated at 200 mg fixed dose every 3 weeks (35). This should provide

more accurate answers to the benefit of pembrolizumab. A similar large phase 2/3 randomized 3 arm trial is comparing pembrolizumab to standard chemotherapy and to the combination thereof (36).

Pemrolizumab is also being evaluated in the neoadjuvant setting for resectable MPM patients in a single-arm phase 1 trial. Patients will receive three cycle of flat dose 200 mg pembrolizumab, followed by surgical resection and adjuvant platinum-pemetrexed chemotherapy (37).

In parallel, there are multiple trials studying the addition of pembrolizumab to other types of treatments. A phase 1 trial is evaluating the safety and efficacy of the addition of pembrolizumab and image-guided resection to surgery and chemotherapy for MPM (38).

Another small phase 1 safety trial is testing adjuvant pembrolizumab after radiation therapy for lung-intact MPM in pre-treated patients (39).

Anti-PD-L1 mAb

PD-L1 blockade works by targeting the tumoral ligand rather than the receptor on T cells, with the same biological rationale as PD-1 inhibition. The phase 1b JAVELIN trial evaluated avelumab, an anti-PD-L1 antibody, in 53 MPM patients who progressed after a platinum-pemetrexed regimen. The ORR was 9% (5 patients), yet disease control rate was 58% and median duration of response was 15.2 months. The ORR was higher in PD-L1-positive tumours (19%) than negative tumours (7%). The most common treatment related toxicity included fatigue, fever, infusion-related reactions, and dermatological side effects and there were 9% Grade 3–4 adverse events. Further studies are warranted for this drug (40).

Different studies are currently ongoing to evaluate another anti-PD-L1 antibody, atezolimumab. A large randomized phase 3 trial is comparing atezolizumab plus bevacizumab and chemotherapy versus bevacizumab and chemotherapy as first-line treatment for advanced MPM (41). Other smaller trials are investigating single-agent atezolizumab post-chemotherapy in MPM, as well as a neoadjuvant study evaluating combined chemo-immunotherapy (42,43).

The single-arm, phase 2, DREAM trial is investigating the combination of the anti-PD-L1 mAb, durvalumab, with first line chemotherapy in MPM. Preliminary results among 54 patients showed an impressive 61% ORR and 71% 6-month PFS rate. However, 57% experienced Grade 3 or greater adverse events (44).

Combination PD-1 and CTLA-4 blockade

The failure of single agent tremelimumab after promising early results led to combination ICI trials in mesothelioma. Tremelimumab was combined with durvalumab, an anti PD-L1 monoclonal antibody in a single-arm phase 2 trial on 40 unresectable mesothelioma patients. There was a 28% ORR, with a median response duration of 16.1 months and a median overall survival of 16.6 months. PD-L1 expression was not predictive of response. 18% of patients had Grade 3–4 treatment-related adverse events (45).

The same combination is under investigation as neoadjuvant therapy. The treatment is administered one to six weeks prior to resection. The primary outcomes are the intratumoral ratio of CD8 T cells to Tregs (CD8/Treg), the percentage of inducible T-cell co-stimulator (ICOS), CD4 T cells and PD-L1 expression (46).

The combination of nivolumab and anti-CTLA4, ipilimumab, has proven its efficacy in melanoma and kidney cancer and is currently under investigation in multiple cancers including mesothelioma. INITIATE, a single arm phase 2 trial of nivolumab and ipilimumab in 34 patients with MPM showed promising results, with 29% PR, a 68% DCR but 34% Grade 3 toxicity (47). Subsequently, the randomized, non-comparative IFCT-1501 MAPS2 evaluated the efficacy and safety of nivolumab and ipilimumab with nivolumab in 125 pre-treated MPM patients. Nivolumab was administered at 3 mg/kg every 2 weeks and in the combination group, ipilimumab was added at 1 mg/kg every 6 weeks. The primary outcome was 3-month DCR. In the intention-to-treat population, the 3-month DCR was 40% versus 52% in the monotherapy versus combination groups, respectively. Grade 3–4 adverse events occurred in 14 % of nivolumab patients and 26% of combination therapy patients, and the latter group also has 3 treatment related deaths. Positive tumour PD-L1 expression (with a cut off of 1%) was associated with increased objective response or disease control in both groups. However, positive PD-L1 tumour expression only led to longer OS in the nivolumab group (48).

This trial thus confirms the results from the other smaller anti PD-L1 trials showing that anti PD- 1 or anti PD-L1 antibodies have activity in patients with MPM. Larger clinical trials are needed to determine whether the combination is better than single agent PD-1 blockade.

Given the efficacy of ICI in subsequent lines of therapy, nivolumab combined with ipilimumab is currently being evaluated in first-line in a randomized phase 3 trial,

Checkmate 743, versus standard first line platinum-pemetrexed chemotherapy in MPM (49).

Non-checkpoint inhibitor immunotherapy: T cell mediated treatments

Innovative cellular therapies are currently under investigation to control MPM, as shown by ongoing clinical trials. These include novel techniques to reactivate the immune. Adoptive cell transfer (ACT) is a type of immunotherapy that entails the collection of the host's immune cells from peripheral blood or the tumour itself, followed by isolation, modification, and *ex vivo* expansion of the targeted immune cells. The modified immune cells are then reinfused into the patient as therapy (50). ACT offers the advantage of targeting effector cells to a specific tumour-associated antigen and leads to direct cytotoxicity. Two of the major categories of ACT are chimeric antigen receptor (CAR) T-cells and TIL infusions.

One approach is to use CARs in order to create a cancer-specific antigen receptor and couple this to effector cells, such as T cells (51). A CAR construct consists of an extracellular antigen-binding domain that is hinged to one or more intracellular signalling domains (52). Once constructed, the CAR is then transduced into autologous T cells and reinjected to the patient as therapy. CARs have been used in acute lymphoblastic leukemia in children with spectacular responses leading to the fast development of this strategy (51). CAR T-cells can have different targets based on antibody and co-stimulatory domains. Mesothelin is a cell-surface glycoprotein over-expressed in up to 95% of patients with epithelioid MPM, though not in the 10–15% of sarcomatoid histotypes (53). It is also be over-expressed in other tumour types. As mesothelin has limited expression in normal tissue, it is a promising cancer-associated antigen target. Furthermore, several preclinical and clinical studies have found that is involved in tumorigenesis, as well as being associated with tumour aggressiveness (54). In preclinical studies, CARs specific against mesothelin were able to decrease tumour size after injection (55). Responses have been mixed, perhaps due to the loss of expression of the targeted antigens (56).

Ongoing phase 1 trials of CAR T-cells in MPM have different designs (*Table 1*) (57-62). In a phase 1 trial, lentiviral transduced mesothelin targeting CAR T-cells are being administered intravenously with or without cyclophosphamide in mesothelin-expressing tumours including metastatic pancreatic cancer, serous epithelial ovarian cancer and MPM (61). Two further phase 1/2 trials are ongoing with intravenous anti-mesothelin CAR T-cells (60,62).

Similarly, mesothelin targeting CAR T-cells are being investigated with intra-pleural infusions in malignant pleural disease arising from lung cancer, breast cancer or MPM. This trial has an additional arm including pembrolizumab, with promising early results with a response in eight out of 11 patients (59).

The second ADT immunotherapeutic strategy we will discuss is the infusion of autologous TILs. TIL therapy initially showed promising efficacy in the treatment of malignant melanoma but its application to other malignancies has presented several challenges. The extraction of sparse tumour-reactive lymphocytes and subsequent isolation and expansion of T-cells that retain specificity and functionality can be challenging (52). Additionally, prolonged clinical response to TIL therapy requires lymphodepletion, with the significant infectious risks it entails (50).

In MPM, there is currently a phase 1/2 trial investigating the safety and efficacy of intravenous autologous TILs after lymphodepletion by cyclophosphamide and fludarabine. After the infusion, patients receive two weeks of low-dose interleukin-2 therapy to promote continued TIL proliferation and activity (63).

Another approach is cancer vaccination. It has been developed by the discovery of tumour associated antigens and involves activating a specific immune response after stimulation through the vaccine. After vaccination, autologous dendritic cells are capable of capturing and processing tumour antigens and express co-stimulatory molecules such as cytokines that will enhance the immune response. Some studies have shown that MPM express high levels of WT1, a protein that regulates gene expression in cancer cells (64). One study is currently recruiting patients to evaluate the effect of a WT1 vaccine associated with platinum-based chemotherapy in front-line treatment in MPM.

Thus, novel ADT strategies appear promising from a scientific perspective, and results of these trials are eagerly awaited, as they could dramatically change the treatment landscape for refractory MPM.

There are currently 21 ongiong trials for MPM evaluating immunotherapy, illustrating the high hopes for these treatments (*Table 1*).

Conclusions

Though MPM is a rare cancer, its incidence is expected to

Table 1 Ongoing trials of immunotherapy in malignant pleural mesothelioma

Experimental therapy	Target	Trial design	Patients	Primary endpoint	Trial status	Clinicaltrials.gov number
Immune checkpoint inhibitors						
Atezolizumab	PD-L1	Phase 1 neoadjuvant cisplatin-pemetrexed with atezolizumab in combination and in maintenance for resectable MPM	28	PFS	Recruiting	NCT03228537
Atezolizumab	PD-L1	Phase 2, single arm, 2nd line atezolizumab after first-line platinum-based chemotherapy	36	ORR	Not yet recruiting	NCT03786419
Atezolizumab and bevacizumab	PD-L1, VEGF	Randomized phase 3: atezolizumab plus bevacizumab and chemotherapy versus bevacizumab and chemotherapy as first-line treatment for advanced MPM	320	PFS, OS	Not yet recruiting	NCT03762018
Pembrolizumab	PD-1	Phase 1, single arm pembrolizumab in combination with chemotherapy and image-guided surgery for MPM	20	Safety	Not yet recruiting	NCT03760575
Pembrolizumab	PD-1	Phase 1: pembrolizumab after radiation therapy versus radiation therapy alone	24	Safety	Recruiting	NCT02959463
Pembrolizumab	PD-1	Phase 2/3, randomized, open label, 3 arm trial: chemotherapy versus chemotherapy plus pembrolizumab versus pembrolizumab alone as front-line treatment	126	PFS	Recruiting	NCT02784171
Pembrolizumab	PD-1	Phase 1, single-arm, neoadjuvant pembrolizumab treatment in patients with resectable MPM	15	PFS	Recruiting	NCT02707666
Pembrolizumab	PD-1	Randomized phase III trial: pembrolizumab versus chemotherapy for advanced pre-treated MPM	144	PFS	Active, not recruiting	NCT02991482
Pembrolizumab	PD-1	Phase II trial of pembrolizumab in MPM	65	Predictive value of PD-L1 on response	Active, not recruiting	NCT02399371
Durvalumab, tremelimumab	PD-L1, CTLA-4	Phase 2, randomized trial, 3 arms, open label: neoadjuvant durvalumab versus durvalumab/tremelimumab versus placebo in resectable MPM	20	Intratumoral ratio of CD8 T cells to regulatory T cells	Recruiting	NCT02592551
Ipilimumab and Nivolumab—Pemetrexed and Cisplatin (CheckMate743)	PD-L1, CTLA-4	Phase 3, randomized, open label trial in front-line unresectable MPM: nivolumab/ipilimumab versus chemotherapy	600	OS, PFS	Active, not recruiting	NCT02899299
Nivolumab	PD-1	Phase 3, randomized trial to evaluate the efficacy of nivolumab in relapsed MPM	336	OS	Recruiting	NCT03063450

Table 1 (*continued*)

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Experimental therapy	Target	Trial design	Patients	Primary endpoint	Trial status	Clinicaltrials.gov number
Rucaparib, abemaciclib, pembrolizumab & bemcentinib, atezolizumab & bevacizumab (MiST)	PARP inhibitor, CDK4/6 inhibitor, PD-1 inhibitor, AXL inhibitor, PD-L1 inhibitor, VEGF inhibitor	Stratified multi-arm phase 2a trial to enable accelerated evaluation of targeted therapies for relapsed MPM	120	DCR at 12 weeks	Active, recruiting	NCT03654833
YS110	CD26	Phase 1/2: single arm, in refractory MPM	47	DCR, PFS	Active, recruiting	NCT03177668
Non checkpoint inhibitor immunotherapy						
TILs, IL2	MPM	Phase 1/2: tumour-infiltrating lymphocytes and low-dose IL-2 therapy following a preparative regimen of non-myeloablative lymphodepletion in second-line MPM treatment	10	Safety	Recruiting	NCT02414945
WT-1 targeted dendritic cell vaccination	WT-1	Phase 1/2 single arm: dendritic cells loaded with mesothelioma-associated tumour antigen WT1 plus conventional chemotherapy in frontline treatment of MPM	20	Feasibility, safety	Recruiting	NCT02649829
Hu-CAR T meso cells	Mesothelin	Phase 1: human CAR modified T cells in patients with mesothelin expressing cancers	30	Safety	Recruiting	NCT03054298
Anti-mesothelin CAR	Mesothelin	Phase 1/2: lymphodepleting regimen and CAR T administration followed by low-dose interleukin-2	15	Safety, response rate	Completed	NCT01583686
Anti-mesothelin CAR	Mesothelin	Phase 1, 2 cohorts: 1 or 3 doses of CAR T cells in MPM	18	Safety, response rate	Completed	NCT01355965
CART-meso	Mesothelin	Phase 1: CAR modified T cells in patients with mesothelin expressing cancers	19	Safety	Completed	NCT02159716
iCasp9M28z T cell infusions	Mesothelin	Phase 1 single arm autologous T cells genetically engineered to target the cancer-cell surface antigen mesothelin	48	Safety	Recruiting	NCT02414269

PFS, progression-free survival; ORR, objective response rate; VEGF, vascular endothelial growth factor; OS, overall survival; PD-1, programmed death protein 1; CTLA-4, cytotoxic T-lymphocyte antigen-4; MPM, malignant pleural mesothelioma; PARP, poly ADP-ribose polymerase; DCR, disease control rate; CAR, chimeric antigen receptor.

peak in next decade. Therefore, given the limited current therapeutic options, identifying safe and effective treatments for this disease is a worthwhile challenge. Immunotherapy, including but not limited to checkpoint inhibition, is a promising and rapidly developing treatment approach.

The role of front-line combination doublet chemotherapy is well established and the benefit of adding an ICI remains to be proven. Similarly, current results do not warrant the use of first-line ICI monotherapy, though large trials are ongoing.

As there is no second-line standard of care, it is tempting to give ICI in this context based on phase 1/2 results. Given current data, single agent anti CTLA-4 therapy is not recommended. On the contrary, PD-1 blockade, as well as combination therapy, are very promising.

Although preliminary data from early studies are encouraging, caution should be exercised, as such results often fail to translate clinical benefit in phase 3 trials. Should these trials confirm their efficacy, the challenge will be analogous to that currently faced in lung cancer: the identification of predictive biomarkers, the choice of ICI and the role and timing of combination therapies. Furthermore, the potential role of CAR T-cells and autologous TIL infusions in MPM will soon be elucidated. Finally, this will have to be integrated with the use other treatment modalities in order to offer the best possible care for mesothelioma patients.

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References

1. Berry G, de Klerk NH, Reid A, et al. Malignant pleural and peritoneal mesotheliomas in former miners and millers of crocidolite at Wittenoom, Western Australia. Occup Environ Med 2004;61:e14.
2. Musk AW, de Klerk NH. Epidemiology of malignant mesothelioma in Australia. Lung Cancer 2004;45 Suppl 1:S21-3.
3. Delgermaa V, Takahashi K, Park EK, et al. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. Bull World Health Organ 2011;89:716-24, 24A-24C.
4. Carbone M, Kratzke RA, Testa JR. The pathogenesis of mesothelioma. Semin Oncol 2002;29:2-17.
5. Robinson M, Wiggins J. Statement on malignant mesothelioma in the UK. Thorax 2002;57:187.
6. Brims FJ, Maskel NA. Prognostic factors for malignant pleural mesothelioma. Current Respiratory Care Reports 2013;2:100-8.
7. Hjerpe A, Ascoli V, Bedrossian CW, et al. Guidelines for the cytopathologic diagnosis of epithelioid and mixed-type malignant mesothelioma: Complementary Statement from the International Mesothelioma Interest Group, Also Endorsed by the International Academy of Cytology and the Papanicolaou Society of Cytopathology. Diagn Cytopathol 2015;43:563-76.
8. Yang H, Testa JR, Carbone M. Mesothelioma epidemiology, carcinogenesis, and pathogenesis. Curr Treat Options Oncol 2008;9:147-57.
9. Hassan R, Alexander R, Antman K, et al. Current treatment options and biology of peritoneal mesothelioma: meeting summary of the first NIH peritoneal mesothelioma conference. Ann Oncol 2006;17:1615-9.
10. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636-44.
11. De Bondt C, Psallidas I, Van Schil PEY, et al. Combined modality treatment in mesothelioma: a systemic literature review with treatment recommendations. Transl Lung Cancer Res 2018;7:562-73.
12. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet 2016;387:1405-14.
13. Tano ZE, Chintala NK, Li X, et al. Novel immunotherapy

clinical trials in malignant pleural mesothelioma. Ann Transl Med 2017;5:245.
14. Ujiie H, Kadota K, Nitadori JI, et al. The tumoral and stromal immune microenvironment in malignant pleural mesothelioma: A comprehensive analysis reveals prognostic immune markers. Oncoimmunology 2015;4:e1009285.
15. Anraku M, Cunningham KS, Yun Z, et al. Impact of tumor-infiltrating T cells on survival in patients with malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2008;135:823-9.
16. Cornelissen R, Lievense LA, Maat AP, et al. Ratio of intratumoral macrophage phenotypes is a prognostic factor in epithelioid malignant pleural mesothelioma. PLoS One 2014;9:e106742.
17. Yamada N, Oizumi S, Kikuchi E, et al. CD8+ tumor-infiltrating lymphocytes predict favorable prognosis in malignant pleural mesothelioma after resection. Cancer Immunol Immunother 2010;59:1543-9.
18. Lizotte PH, Jones RE, Keogh L, et al. Fine needle aspirate flow cytometric phenotyping characterizes immunosuppressive nature of the mesothelioma microenvironment. Sci Rep 2016;6:31745.
19. Chene AL, d'Almeida S, Blondy T, et al. Pleural Effusions from Patients with Mesothelioma Induce Recruitment of Monocytes and Their Differentiation into M2 Macrophages. J Thorac Oncol 2016;11:1765-73.
20. Calabro L, Morra A, Fonsatti E, et al. Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. Lancet Oncol 2013;14:1104-11.
21. Calabro L, Morra A, Fonsatti E, et al. Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. Lancet Respir Med 2015;3:301-9.
22. Calabro L, Ceresoli GL, di Pietro A, et al. CTLA4 blockade in mesothelioma: finally a competing strategy over cytotoxic/target therapy? Cancer Immunol Immunother 2015;64:105-12.
23. Maio M, Scherpereel A, Calabrò L, et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. Lancet Oncol 2017;18:1261-73.
24. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
25. Zhang Y, Huang S, Gong D, et al. Programmed death-1 upregulation is correlated with dysfunction of tumor-infiltrating CD8+ T lymphocytes in human non-small cell lung cancer. Cell Mol Immunol 2010;7:389-95.
26. Awad MM, Jones RE, Liu H, et al. Cytotoxic T Cells in PD-L1-Positive Malignant Pleural Mesotheliomas Are Counterbalanced by Distinct Immunosuppressive Factors. Cancer Immunol Res 2016;4:1038-48.
27. Cedres S, Ponce-Aix S, Pardo-Aranda N, et al. Analysis of expression of PTEN/PI3K pathway and programmed cell death ligand 1 (PD-L1) in malignant pleural mesothelioma (MPM). Lung Cancer 2016;96:1-6.
28. Khanna S, Thomas A, Abate-Daga D, et al. Malignant Mesothelioma Effusions Are Infiltrated by CD3(+) T Cells Highly Expressing PD-L1 and the PD-L1(+) Tumor Cells within These Effusions Are Susceptible to ADCC by the Anti-PD-L1 Antibody Avelumab. J Thorac Oncol 2016;11:1993-2005.
29. Mansfield AS, Roden AC, Peikert T, et al. B7-H1 expression in malignant pleural mesothelioma is associated with sarcomatoid histology and poor prognosis. J Thorac Oncol 2014;9:1036-40.
30. Quispel-Janssen J, van der Noort V, de Vries JF, et al. Programmed Death 1 Blockade With Nivolumab in Patients With Recurrent Malignant Pleural Mesothelioma. J Thorac Oncol 2018;13:1569-76.
31. Goto Y, Okada, M., Kijima, T., et al. A phase ii study of nivolumab: a multicenter, open-label, single arm study in malignant pleural mesothelioma (MERIT). Association for the Study of Lung Cancer 18th World Conference on Lung Cancer; Yokohama, Japan2017.
32. ClinicalTrials.gov. CheckpOiNt Blockade For Inhibition of Relapsed Mesothelioma (CONFIRM). 2018, July 24. Available online: https://clinicaltrials.gov/ct2/show/NCT03063450.
33. Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. Lancet Oncol 2017;18:623-30.
34. Desai A, Karrison T, Rose B, et al. OA08.03 Phase II Trial of Pembrolizumab (NCT02399371) In Previously-Treated Malignant Mesothelioma (MM): Final Analysis. J Thorac Oncol 2018;13:S339.
35. ClinicalTrials.gov. PembROlizuMab Immunotherapy Versus Standard Chemotherapy for Advanced prE-treated Malignant Pleural Mesothelioma (PROMISE-meso). 2018, June 26. Available online: https://clinicaltrials.gov/ct2/show/NCT02991482

36. ClinicalTrials.gov. Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma. 2019, April 10. Available online: https://clinicaltrials.gov/ct2/show/NCT02784171.
37. ClinicalTrials.gov. A Pilot Window-Of-Opportunity Study of the Anti-PD-1 Antibody Pembrolizumab in Patients With Resectable Malignant Pleural Mesothelioma. 2018, January 4. Available online: https://clinicaltrials.gov/ct2/show/record/NCT02707666
38. ClinicalTrials.gov. Pembrolizumab in Combination With Chemotherapy and Image-Guided Surgery for Malignant Pleural Mesothelioma (MPM). 2019, April 16. Available online: https://clinicaltrials.gov/ct2/show/NCT03760575
39. ClinicalTrials.gov. Adjuvant Pembrolizumab After Radiation Therapy for Lung-Intact Malignant Pleural Mesothelioma. 2019, March 5. Available online: https://clinicaltrials.gov/ct2/show/NCT02959463
40. Hassan R, Thomas A, Nemunaitis JJ, et al. Efficacy and Safety of Avelumab Treatment in Patients With Advanced Unresectable Mesothelioma: Phase 1b Results From the JAVELIN Solid Tumor Trial. JAMA Oncol 2019. [Epub ahead of print].
41. ClinicalTrials.gov. Atezolizumab With Bevacizumab and Chemotherapy vs Bevacizumab and Chemotherapy in Early Relapse Ovarian Cancer. 2018, December 18. Available online: https://clinicaltrials.gov/ct2/show/NCT03353831
42. ClinicalTrials.gov. A Study of Atezolizumab in Unresectable or Advaced Malignant Pleural Mesothelioma. 2018, December 25. Available online: https://clinicaltrials.gov/ct2/show/NCT03786419
43. ClinicalTrials.gov. Atezolizumab, Pemetrexed Disodium, Cisplatin, and Surgery With or Without Radiation Therapy in Treating Patients With Stage I-III Pleural Malignant Mesothelioma. 2019, May 1. Available online: https://clinicaltrials.gov/ct2/show/NCT03228537
44. Nowak AK, Lesterhuis WJ, Hughes B, et al. DREAM: A phase II study of durvalumab with first line chemotherapy in mesothelioma—First results. J Clin Oncol 2018;36:8503.
45. Calabro L, Morra A, Giannarelli D, et al. Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2 study. Lancet Respir Med 2018;6:451-60.
46. ClinicalTrials.gov. MEDI4736 Or MEDI4736 + Tremelimumab In Surgically Resectable Malignant Pleural Mesothelioma. 2019, January 16. Available online: https://clinicaltrials.gov/ct2/show/NCT02592551
47. Disselhorst MJ, Quispel-Janssen J, Lalezari F, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. Lancet Respir Med 2019;7:260-70.
48. Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. Lancet Oncol 2019;20:239-53.
49. ClinicalTrials.gov. Study of Nivolumab Combined With Ipilimumab Versus Pemetrexed and Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma Patients (CheckMate743). 2019, April 29. Available online: https://clinicaltrials.gov/ct2/show/NCT02899299
50. Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science 2015;348:62-8.
51. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385:517-28.
52. Sadelain M, Brentjens R, Riviere I. The basic principles of chimeric antigen receptor design. Cancer Discov 2013;3:388-98.
53. Baldo P, Cecco S. Amatuximab and novel agents targeting mesothelin for solid tumors. Onco Targets Ther 2017;10:5337-53.
54. Servais EL, Colovos C, Rodriguez L, et al. Mesothelin overexpression promotes mesothelioma cell invasion and MMP-9 secretion in an orthotopic mouse model and in epithelioid pleural mesothelioma patients. Clin Cancer Res 2012;18:2478-89.
55. Adusumilli PS, Cherkassky L, Villena-Vargas J, et al. Regional delivery of mesothelin-targeted CAR T cell therapy generates potent and long-lasting CD4-dependent tumor immunity. Sci Transl Med 2014;6:261ra151.
56. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507-17.
57. O'Hara M, Stashwick C, Haas AR, et al. Mesothelin as a target for chimeric antigen receptor-modified T cells as anticancer therapy. Immunotherapy 2016;8:449-60.
58. Klampatsa A, Haas AR, Moon EK, et al. Chimeric Antigen Receptor (CAR) T Cell Therapy for Malignant Pleural Mesothelioma (MPM). Cancers (Basel) 2017;9. doi: 10.3390/cancers9090115.
59. ClinicalTrials.gov. Malignant Pleural Disease Treated With Autologous T Cells Genetically Engineered to

Target the Cancer-Cell Surface Antigen Mesothelin. 2019, May 17. Available online: https://clinicaltrials.gov/ct2/show/NCT02414269
60. ClinicalTrials.gov. CAR T Cell Receptor Immunotherapy Targeting Mesothelin for Patients With Metastatic Cancer. 2019, May 22. Available online: https://clinicaltrials.gov/ct2/show/NCT01583686
61. ClinicalTrials.gov. CART-meso in Mesothelin Expressing Cancers. 2019, February 26. Available online: https://clinicaltrials.gov/ct2/show/NCT02159716.
62. ClinicalTrials.gov. Autologous Redirected RNA Meso-CIR T Cells. 2017, September 19. Available online: https://clinicaltrials.gov/ct2/show/NCT01355965
63. ClinicalTrials.gov. TILs & Low-Dose IL-2 Therapy Following Cyclophosphamide and Fludarabine in Pleural Mesothelioma Patients. 2019, February 5. Available online: https://clinicaltrials.gov/ct2/show/NCT02414945
64. Thomas A, Hassan R. Immunotherapies for non-small-cell lung cancer and mesothelioma. Lancet Oncol 2012;13:e301-10.

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