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Malignant Pleural Mesothelioma: Is Tailoring the Second-Line Therapy Really "Raising the Bar?"

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Opinion statement

Unresectable or relapsed malignant pleural mesothelioma (MPM) has dismal prognosis. First-line combination therapy with pemetrexed and a platinum analog allows a modest survival benefit, while no clear therapeutic options exist for the second-line therapy. In this setting, pemetrexed seems to be the most active drug; however, the inclusion in front-line treatment limits its use in further lines. Nevertheless, rechallenge with one or both drugs used in first-line remains a feasible strategy for responder patients. Alternatively, only few cytotoxic drugs have demonstrated a mild activity in refractory MPM.

Among other options, targeted therapy has unfortunately produced disappointing results as salvage treatment probably due to the lack of a clear understanding of the tumor biology. In contrast, recent data suggest moderate efficacy and mild toxicity of immunotherapy also for the treatment of MPM. The combination of checkpoint inhibitors with chemotherapy or other immunological agents seems promising and could really "raise the bar" in this setting.

Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumor of the pleura characterized by a poor prognosis with an overall 5-year survival rate of 8.5% [1]. Asbestos exposure is the leading cause of MPM through induction of chronic inflammation. In fact, after phagocyting asbestos fibers, macrophages release reactive oxygen species which are potent DNA-mutagenic agents [2]. Other risk factors for developing mesothelioma are occupational radiation and prior chest radiation therapy [3]. Rare cases of familial mesothelioma have been related to a germline mutation in breast-related cancer antigens (BRCA)–associated protein 1 (BAP1), involved in regulation of gene expression and DNA repair [4]. The histological classification of MPM includes three subtypes: epithelioid, sarcomatoid (including desmoplastic and lymphohistiocytic variants), and biphasic. Epithelioid histology is associated with a more favorable prognosis and occurs in 50–60% of patients, whereas the sarcomatoid subtype (20% of cases) has a poor prognosis with a lower chance of response to therapy.

Multimodality therapy with systemic chemotherapy, surgical resection, and sometimes radiation therapy are generally offered to young patients with good performance status, localized disease, and epithelioid histological subtype [5, 6]. Surgical options consist of pleurectomy/decortication with mediastinal lymph node sampling or extrapleural pneumonectomy. Radiation therapy can relieve symptoms in advanced disease, while its role after an incomplete surgical resection is still controversial due to high toxicity to the intact lung [7].

Unfortunately, most patients with MPM present with advanced stage disease or are not eligible for surgical resection because of relevant comorbidities and/or advanced age. Systemic therapy represents the only treatment for these patients, allowing a median survival of approximately 1 year [8]. The phase III EMPHACIS trial demonstrated that combination therapy with cisplatin (CDDP) and pemetrexed (PEM) is charily superior to CDDP alone in chemo-naïve patients with MPM in terms of response rate (RR) (41.3% vs 13.7%), progression-free survival (PFS) (5.7 vs 3.9 months, p=0.001), and overall survival (OS) (12.1 vs 9.3 months, p=0.02) [9]. The carboplatin-PEM regimen showed comparable efficacy to CDDP-PEM in a phase II study, so it may be preferred in patients with a poor performance status (PS) and/or comorbidities [10]. Based on these results, the combination of a platinum analog (cisplatin or carboplatin) with PEM is considered the current standard for first-line therapy in unresectable MPM. CDDP-gemcitabine doublet might be an alternative regimen, even if it has been evaluated only in phase II studies with very heterogeneous results (response rates ranging 12–48% and median OS 9.5–12 months) [11–15]. The combination of raltitrexed, another antimetabolite agent, with CDDP improved overall survival compared with CDDP alone (11.4 vs 8.8 months) without detrimental effect on the quality of life, as reported in the EORTC trial, including untreated patients with MPM [16].

Anti-angiogenic agents have been evaluated in addition to standard platinum doublets in order to improve outcome of first-line systemic treatment. In particular, the addition of bevacizumab to CDDP-PEM significantly prolongs median OS (mOS) in comparison to CDDP-PEM (18.8 vs 16.1 months) [17]. Despite the increase of overall grade 3–4 toxicity and recurrence of class-specific adverse events, the combination of bevacizumab-CDDP-PEM has been recommended in NCCN guidelines (category 2A) for first-line treatment of MPM [18]. In the phase III part of LUME-Meso trial, the combination of CDDP-PEM with nintedanib, an anti-angiogenic multikinase inhibitor, produced a significant improvement of the primary endpoint PFS in comparison to chemotherapy alone (hazard ratio [HR] 0.56; 95%CI 0.34 to 0.91; p=0.017) [19]. However, the advantage in mOS was not statistically significant (HR 0.77; 95%CI 0.46 to 1.29; p=0.319), even in the subgroup of patients

with epithelioid histology, who however experienced the major survival benefit (mOS 20.6 months vs 15.2 months; p=0.197). A phase III study on epithelioid histology population started recruitment in March 2016 and is currently ongoing.

In contrast with the success obtained in non-small cell lung cancer, the switch maintenance strategy failed to improve survival in MPM patients, probably for the employment of drugs without a demonstrated efficacy in this disease. In fact, the phase II randomized trial (COMMAND) compared a FAK (focal adhesion kinase) inhibitor, defactinib, with placebo as maintenance treatment after first-line platinum-pemetrexed therapy [20]. Unfortunately, no differences in efficacy were found between the two arms; thus, the trial was early stopped for futility.

While the platinum-pemetrexed–based regimens are considered the cornerstone of first-line treatment of MPM, the clinical role of second-line therapy is still controversial. Here, we review the second-line options of treatment for MPM, moving from actual therapeutic strategies to promising future approaches.

Cytotoxic agents

The effect of post-study chemotherapy (PSC) was retrospectively analyzed in 191 patients (42%) of the EMPHACIS trial. Patients from both arms who had received PSC after the front-line treatment had a better survival compared to no-PSC patients, with an HR of 56% (CI 0.44–0.72; p<0.001), adjusted for baseline prognostic factors and treatment intervention [21]. The retrospective nature of this not preplanned analysis does not allow definitive conclusions, because it cannot be excluded that patients with prolonged survival tend to receive more treatments. However, this study suggests that second-line treatment is feasible and probably active at least in a subgroup of patients with MPM. Before the combination CDPP-PEM becoming the standard therapy in first-line, a phase III trial of Jassem et al. [22] demonstrated a benefit with PEM monotherapy in terms of RR, disease control rate (DCR), and PFS but not OS in comparison with placebo. However, the wide use of pemetrexed in front-line therapy and the absence of OS advantage in second-line make the use of PEM as post-progression treatment clinically insignificant.

Current options for patients who had disease progression after first-line therapy, while maintaining a fairly good PS, are either rechallenge with the same front-line drugs or second-line treatment with other active drugs, such as gemcitabine and vinorelbine.

Rechallenge therapy was more supported by experience maturated in other tumors sensitive to platinum compounds, as ovarian cancer, rather than by studies on MPM. In fact, no randomized trial has been conducted focusing on retreatment with one or both drugs from the combination of CDPP-PEM used in first-line. Second-line therapy with PEM is under evaluation in comparison with BSC in a phase III randomized trial (NCT00190762), but only PEM-naïve patients are included. Ceresoli et al. evaluated pemetrexed-based retreatment in an observational study conducted on 31 patients who had obtained a PFS greater than 3 months with first-line therapy [23]. Sixteen patients received rechallenge with PEM/platinum combination while 15 patients were retreated with PEM as a single agent. The response rate was 19% with one complete response and 5 partial responses; the DCR was 48%. A PFS of 3.8 months was reached in the overall population; PFS was longer (5.5 months) in patients with a first-line PFS >12 months. Furthermore, the rechallenge treatment was well

tolerated; grade 3 or 4 hematological toxicity occurred only in 9.7% of patients. In a retrospective case series of 181 patients who received a second-line treatment from 1996 to 2008, 42 patients were retreated with a pemetrexed-based chemotherapy; in particular, 31 patients received a pemetrexed/platinum doublet and 11 patients pemetrexed alone. Among PEM-treated patients, both PFS (6.4 months vs 2.4 months, p=0.003) and OS (13.4 months vs 4.2 months, p<0.001) were significantly longer in those treated with PEM/platinum combination compared with the subgroup receiving pemetrexed alone [24]. Otherwise, the DCR was high in both subgroups but not significantly different (74.2% vs 60.0%; p=0.441). The interpretation of these results is difficult due to the retrospective nature of the study with probable selection bias and inclusion of some patients not previously exposed to PEM; moreover, the choice of treatment in the PEM-group may have been influenced either by PS or age.

Among other chemotherapy agents, vinorelbine and gemcitabine have been evaluated for second-line treatment of MPM. In a phase II open-label study, only 63 patients with previous exposure to chemotherapy were treated with weekly vinorelbine after disease relapse [25]. Ten partial responses (16%) and 43 stable diseases (68%) were observed with an overall survival of 9.6 months (95%CI 7.3–118 months). Even in this case, a selection bias could have influenced the results. In fact, the study population seems to have more favorable clinical characteristics compared with real-life patients, including the median age (59 years), the median time from the end of first-line therapy to the start of the study treatment (6 months), and the good ECOG PS. A randomized phase II trial (NCT02139904) is evaluating weekly vinorelbine after the failure of first-line standard platinum-based chemotherapy with active symptom control as comparator arm. GEM alone or GEM-based chemotherapy was the most common second-line therapy in the retrospective analysis of PSC in the EMPHACIS trial [21]. However, the contribution of GEM to the survival advantage observed in this study cannot be extrapolated. In a retrospective study including patients from 4 Turkish institutions, the efficacy of second-line GEM was assessed [26]. Median OS was 11.3 months in GEM-treated patients in comparison with 9.9 months in patients not receiving chemotherapy (p=0.056), but the 3-year survival rate was significantly higher in GEM-treated patients (14% vs 0%, p=0.005).

Combination therapy has been explored in second-line treatment with some encouraging results (Table 1). In particular, a not-negligible activity was reported with gemcitabine and vinorelbine (RR 10%, OS 10.9 months, PFS

Table 1. Combination of cytotoxic drugs for second-line treatment of malignant pleural mesothelioma

Author, year	N. patients	First-line therapy	Second-line therapy	RR (%)	mTTP	mOS
Fennell, 2007 [29]	13	CT	IPM	20	n.r.	7.3
Okuno, 2008 [28]	23	CT	GEM1000+EPI	13	6.3	9.3
	45	CT	GEM750+EPI	7	4.2	5.7
Zucali, 2008 [27]	30	CDDP + PEM	GEM + VNL	10	2.8	10.3

CT, chemotherapy; *CDDP*, cisplatin; *IMP*, irinotecan + cisplatin + mitomicin C; *GEM*, gemcitabine; *EPI*, epirubicin; *mOS*, median overall survival; *mTTP*, median time to progression; *n.*, number; *n.r.*, not reported; *PEM*, pemetrexed; *RR*, response rate; *VNL*, vinorelbine

2.8 months) [27]; gemcitabine and epirubicin (RR 13%, OS 9.3 months, PFS 6.3 months in a high-dose group) [28]; irinotecan, cisplatin, and mitomycin (RR 20%, OS 7.3 months, PFS 7.3 months) [29]. The use of these combination treatments in clinical practice was hampered by the related toxicity, especially in frail and pretreated patients. With the possible exclusion of the doublet GEM-vinorelbine, which was well tolerated, the usefulness of combination therapy in the practice is hampered by potential toxicity, especially in elderly and frail patients.

In conclusion, the role of second-line cytotoxic therapy for MPM remains not clearly defined. We are waiting for the results of several ongoing single-arm phase II studies aimed at assessing the efficacy of cytotoxic drugs, such as GEM, EPI, and alkaloid agents, alone or in combination with novel agents, in pre-treated patients (Table 2). Enrollment has been completed in many of them and results might be soon available.

Targeted therapy

Several targeted therapies have been evaluated for the salvage treatment of mesothelioma, including drugs which target the angiogenic pathway by inhibition of platelet-derived growth factor receptor (PDGF-R) and vascular endothelial growth factor receptor (VEGF-R), and their ligands. Indeed, high levels of vascular endothelial growth factor (VEGF) were found in MPM patients, suggesting an important role of angiogenesis in the proliferation of mesothelioma tumor cells [30].

A phase II trial evaluating the combination of bevacizumab and erlotinib, an epithelial growth factor receptor (EGFR) tyrosine kinase inhibitor, was stopped early after the enrollment of 24 patients because none of the 2 preplanned responses were observed, although safety profile was acceptable [31]. In another two-stage phase II study, the PF-03446962 trial, a new anti-angiogenic monoclonal antibody directed against activin receptor-like kinase 1 was tested, but neither response nor stable disease was achieved in MPM patients with progressive disease after platinum-based chemotherapy [32].

NGR-hTNF is an antitumor recombinant protein, specifically a modified tumor necrosis factor alpha (TNFα), able to increase intratumoral chemotherapy penetration and T cell infiltration through a vessel normalization. A phase 3 trial including 400 patients with refractory MPM compared the combination of NGR-hTNF and single-agent chemotherapy (gemcitabine, vinorelbine, or doxorubicin) with chemotherapy alone. Although, OS, the primary endpoint, did not significantly differ between the two treatment arms, a significant interaction between treatment and treatment-free interval (TFI) after first-line therapy was found. In particular, patients with short TFI (<median 4.8 months) had better OS and PFS with the addition of NGR-hTNF to chemotherapy. Interestingly, this survival benefit was maintained after a 3-year follow-up, deserving of a confirmatory randomized trial including only these patients having a poor prognosis [33, 34].

Cediranib is an oral small-molecule inhibitor of VEGF-R1-3, PDGF-R-b, and Kit proto-oncogene receptor tyrosine kinase (C-KIT). Response rates of 10% and 34% of stable disease were reported in a phase II trial involving 51 mainly pretreated patients who received cediranib at 45 mg daily [35]. The prespecified

Table 2. Key ongoing phase II and III clinical trials evaluating cytotoxic drugs in pretreated malignant pleural mesothelioma

Phase	Study drug(s)	Drug(s) class	Clinical trial title	Clinical trial number	Estimated enrolment	Primary endpoint	Status	Start date
III, randomized	Doxorubicin hydrochloride vs ranpirnase	Anthracycline + ribonuclease enzyme	ONCONASE Plus Doxorubicin Versus Doxorubicin Alone For Patients With Malignant Pleural or Peritoneal Mesothelioma Who Have Had No More Than One Prior Chemotherapy Regimen	NCT00003034	300	OS	Unknown	May 1997
II, randomized	Vinorelbine vs BSC	Vinca alkaloid	A Randomised Phase II Trial of Oral Vinorelbine as Second Line Therapy for Patients With Malignant Pleural Mesothelioma	NCT02139904	200	OS	Recruiting participants	March 1, 2016
II, single arm	Trabectedin	Alkaloid	ATREUS Trial - A Phase II Study on the Activity of Trabectedin of Pretreated Epithelioid or Biphasic / Sarcomatoid Malignant Pleural Mesothelioma (MPM)	NCT02194231	141	12 weeks PFS rate	Recruiting	July 2013
II, single arm	Lurbinectedin	Alkaloid	Lurbinectedin Monotherapy in Patients With Progressive Malignant Pleural Mesothelioma. A Multicenter, Single-arm Phase II Trial	NCT03213301	43	12 weeks PFS rate	Recruiting	September 28, 2017
II, single arm	Cisplatin, methotrexate, and gemcitabine	Inhibitor of tumoral DNA synthesis + nucleoside analogue	A Phase 2 Study of Transarterial Chemoperfusion Treatment With Cisplatin, Methotrexate and Gemcitabine in Patients With Unresectable Pleural Mesothelioma	NCT02611037	36	DCR	Recruiting	January 4, 2016
II, single arm	Gemcitabine and cisplatin	Nucleoside analogue + inhibitor of tumoral DNA synthesis	Phase II Study of Six Hours Low Dose Gemcitabine Plus Cisplatin in the Treatment for Advanced Pleural Mesothelioma	NCT01869023	26	2 years PFS rate	Active, not recruiting	November 2010
II, single arm	Milataxel	Taxol-analog	An Efficacy Study of Milataxel (TL139) Administered Orally for Malignant Mesothelioma	NCT00685204	90	RR	Unknown	March 2008
II, single arm	Mithramycin	Inhibitor of cancer stem cell signaling	Phase II Evaluation of Mithramycin, an Inhibitor of Cancer Stem Cell Signaling, in Patients With Malignancies Involving Lungs, Esophagus, Pleura, or Mediastinum	NCT01624090	57	RR	Recruiting	June 13, 2012

Table 2. (Continued)

Phase	Study drug(s)	Drug(s) class	Clinical trial title	Clinical trial number	Estimated enrolment	Primary endpoint	Status	Start date
II, single arm	Mithramycin	Inhibitor of cancer stem cell signaling	Phase I/II Evaluation of Continuous 24 h Intravenous Infusion of Mithramycin, an Inhibitor of Cancer Stem Cell Signaling, in Patients With Primary Thoracic Malignancies or Carcinomas, Sarcomas or Germ Cell Neoplasms With Pleuropulmonary Metastases	NCT02859415	100	MTD; RR	Recruiting	August 6, 2016

BSC, basic supportive care; *OS*, overall survival; *PFS*, progression-free survival; *RR*, response rate; *TTP*, time to progression; *DCR*, disease control rate; *MTD*, maximum tolerated dose

primary endpoint of 25% RR was not reached; mPFS of 1.8 months and mOS of 4.4 months were disappointing as well as tolerability, which required a dose reduction to 30 mg daily after the first 15 patients enrolled.

Sorafenib, a tyrosine kinase inhibitor of RAS/MEK pathway, VEGF-R, PDGF-R, and C-KIT, showed a mild activity in a phase II study of Cancer and Leukemia Group including 51 patients who had received until one prior chemotherapy regimen. Only 3 patients (6%) had a partial response and the other 27 (54%) a stable disease with a sorafenib dose of 400 mg twice a day [36]. Median PFS and mOS were 3.6 and 9.7 months, respectively. Another phase II study evaluated the same dose of sorafenib in pretreated patients using Simon's two-stage design with PFS at 6 months as primary endpoint [37]. Despite the RR of 6% with stable disease obtained in 56% of cases, mPFS was 5.1 months and the preplanned proof of efficacy was reached, being 36% of patients progression-free at 6 months.

Sunitinib, another inhibitor of multiple tyrosine kinase receptors including VEGF-R1-3, was also studied in two cohorts of patients of a phase II trial with a two-stage design [38]. Efficacy results were very poor, so neither the cohort of previously untreated (18 patients) nor that of pretreated patients (17 patients) met the criteria for continuing to the second stage of accrual.

Elevated expression level evaluated by immunohistochemistry (IHC) analysis of PDGF-R-a and PDGF-R-b and their ligands, as well as PDGF-AA and PDGF-BB, was observed on mesothelioma cells [39]. Based on these findings, imatinib, the PDGF-R and c-KIT inhibitor used for treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors, has been tested as salvage therapy in mesothelioma. While no activity was observed as a single-agent therapy [40, 41], the combination with cytotoxic drugs seems to be more promising. In fact, preclinical studies reported that imatinib may facilitate the drug penetration into tumor mass by reducing the interstitial tumor tissue pressure [42]. A phase I trial demonstrated a partial response in 1 out 5 chemorefractory patients who received the combination of imatinib and gemcitabine [43]. The same combination is now under evaluation in a phase II trial recruiting patients who had disease progression after pemetrexed-based regimens (NCT02303899).

A new c-KIT and VEGFR-2 inhibitor, semaxanib, was evaluated as a second-line therapy in a phase II trial enrolling 23 patients. Although a not-negligible antitumor activity was observed with a RR of 11% and stable disease obtained in 33% of patients, the severe toxicity profile related to this drug precluded its further development for mesothelioma. In fact, hyperglycemia and lymphopenia occurred in 19% of patients and thrombosis in 14% of cases with numerous cardiovascular events [44].

Everolimus, the inhibitor of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway used in several types of cancer (metastatic breast cancer, renal cell carcinoma, neuroendocrine tumors), showed only a limited clinical activity, considered as not sufficient for further investigations, in a phase II study involving previously treated MPM patients [45]. Also, the proteasome inhibitor bortezomib failed to show relevant clinical activity for relapsed mesothelioma, as observed in a phase II study including 23 patients. In fact, only one partial response and one stable disease were achieved [46].

The elevated frequency (57–63%) of *BAP1* mutations found in MPM has increased the interest in targeting the gene expression regulation [47].

Vorinostat is a histone deacetylase inhibitor, which was investigated in a large phase III trial (VANTAGE-014) with OS as primary endpoint [48]. Six hundred sixty-one patients with advanced MPM who had previously failed 1 or 2 chemotherapy regimens were randomized to vorinostat vs placebo. Despite a statistically but not clinically significant improvement of PFS from 6.1 to 6.3 weeks (HR 0.75, 95%CI 0.63–0.88; $p<0.001$), there was no significant benefit in terms of OS. In fact, mOS in the vorinostat arm was 30.7 vs 27.1 weeks in the placebo arm (HR 0.98; 95%CI 0.83–1.17; $p=0.86$). Also belinostat, another histone deacetylase inhibitor, did not show any clinical activity. No responses were observed in a phase II study involving pretreated MPM patients [49].

Although these studies failed to demonstrate a clinical benefit through the inhibition of histone deacetylase to target epigenetic regulation in MPM, a preclinical study founded synthetic lethality with pharmacologic inhibition of enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) in MPM cells lacking BAP1 [50]. The EZH2 inhibitor tazemetostat was evaluated in a multipart phase II study including patients affected by relapsed or refractory MPM with both *BAP1*-deficient and wild-type (NCT02860286). Preliminary results were recently reported at the 2018 ASCO Meeting. In the first part, safety was assessed in a cohort of 13 patients unselected for BAP1 expression. No drug discontinuations due to adverse events were observed. The most frequently reported side effects of any grade were the following: fatigue (32%), decreased appetite (28%), dyspnea (28%), and nausea (27%). The second part of the study evaluated the clinical activity in a cohort of 61 patients with inactive BAP1, using a two-stage design. The Stage 2 disease control rate criterion of ≥35% was surpassed, with 31 patients (51%) achieving disease control at 12 weeks and 15 patients (25%) sustaining disease control at 24 weeks. Considering the acceptable safety profile and the interesting clinical activity, tazemetostat is worthy to be evaluated in a larger clinical trial [51].

Aurora kinases are targetable proteins which regulate the mitotic spindle assembly. Their expression is upregulated in more aggressive mesotheliomas [52]. Alisertib is a selective aurora kinase A inhibitor under investigation in an ongoing phase II trial (NCT02293005) recruiting patients with MPM refractory with at least one prior therapy. The 4-months PFS is the primary outcome. Based on preliminary results presented at the Santa Monica International Association for the Study of Lung Cancer meeting in February 2016 [53], alisertinib is well tolerated with very few rates of grade 3 events and without any grade 4 events; several patients obtained disease control for an interval longer than 4 months.

Mesothelioma tumor cells express a surface protein, mesothelin, at a higher level than normal mesothelial cells. Although the function of mesothelin is unknown, this surface protein has been exploited as a therapeutic target [54]. Various antibody-drug conjugates directed to mesothelin have been developed, including anetumab ravtansine, an anti-mesothelin antibody conjugated with the maytansinoid DM4, an inhibitor of microtubule polymerization [55]. A randomized phase II trial failed to demonstrate a benefit in terms of PFS in favor of this new agent compared with vinorelbine in pretreated MPM patients [56]. The safety and activity of the anetumumab ravtansine in combination with pembrolizumab are currently being investigated in a phase I–II trial (NCT03126630) comparing the combined treatment with anetumumab ravtansine alone.

Transforming growth factor-beta (TGFβ) promotes tumor growth and metastases and suppresses host antitumor immunity. GC1008 is a human anti-TGFβ monoclonal antibody that neutralizes all isoforms of TGFβ. Unfortunately, a phase II trial of GC1008 in pretreated MPM patients was stopped early by the manufacturer which discontinued the development of the antibody for oncology indications. However, no partial responses were observed in 13 enrolled patients [57].

The ligand insulin-like growth factor (IGF) helps tumor cells grow and divide. Insulin-like growth factor receptor (IGFR) is also expressed in MPM. Cixutumumab is a monoclonal antibody against IGFR with antitumoral activity. Even in this case, no clinical activity was observed in 20 pretreated MPM patients enrolled in a phase II study [58].

SS1P is a recombinant immunotoxin, which consists of an anti-mesothelin moiety linked to a portion of Pseudomonas endotoxin A. This novel agent has been evaluated in a pilot trial including 10 patients with chemotherapy-refractory mesothelioma [59]. The patients also received pentostatin and cyclophosphamide in order to delay the development of neutralizing antibody direct to the pseudomonas endotoxin. Three patients experienced major tumor regression, 3 had stable disease, and 4 progressive disease.

The ongoing phase II and phase III trials evaluating targeted therapies are reported in Table 3. The trial on targeted therapy that met the primary endpoint is summarized in Table 4.

Immunotherapy

The immune checkpoint inhibitors, targeting the cytotoxic lymphocyte antigen 4 (CTLA4) and programmed Death-1/Programmed Death-Ligand 1 (PD-1/PD-L1) signaling axis, have been approved for the treatment of several tumor types, such as melanoma, non-small-cell lung cancer, renal cancer, and head and neck cancer [60]. PD-L1 IHC expression seems to be a negative prognostic tissue biomarker for MPM patients, as showed in a study of Mansfield et al. In their study, 106 patients were assessed for PD-L1 expression by IHC. Forty-two (40%) patients with positive PD-L1 were less likely to undergo therapeutic surgery and had a worse survival than those with negative (mOS 5.0 vs 14.5 months; $p<0.0001$) [61]. Several clinical trials are still investigating the role of the immunotherapy in MPM treatment (Table 5). The studies with available results are listed in Table 6.

Tremelimumab is a monoclonal antibody direct to CTLA-4, a checkpoint inhibitor receptor of lymphocyte T activated by the costimulatory molecules, B7.1 and B7.2, expressed on dendritic cells. The blockage of CTLA-4 pathway enhances T cell activation and anti-tumor effects. A single-arm phase II study evaluated the efficacy and safety of tremelimumab given at a dose of 15 mg/kg every 90 days [62]. Twenty-nine MPM patients who had experienced a progression of disease after a front-line platinum-based regimen were enrolled. Two patients had a PR (7%), one of which occurred after initial progression; 9 patients achieved stable disease. Median PFS and mOS were 6.2 months and 10.7 months, respectively. Despite these encouraging results, the target response rate of 17%, fixed as the primary endpoint, was not met. Furthermore, grade 1–2 adverse events occurred in 93% of patients; the most frequent were

Table 3. Key ongoing phase II and III clinical trials evaluating targeted drugs in pretreated malignant pleural mesothelioma

Phase	Study drug(s)	Drug(s) class	Clinical trial title	Clinical trial number	Estimated enrolment	Primary endpoint	Status	Start date
II, single arm	Gemcitabine and imatinib mesylate	Cytotoxic drug chemotherapy, tyrosine kinase inhibitor (anti-PDGFR)	A Phase II Study of the Combination of Gemcitabine and Imatinib Mesylate in Pemetrexed-pretreated Patients With Malignant Pleural Mesothelioma	NCT02303899	22	3 months PFS rate	Ongoing, but not recruiting participants	November 2014
II, single arm	Alisertib	Aurora kinase A inhibitor	Phase II Trial of Alisertib (MLN8237) in Salvage Malignant Mesothelioma	NCT02293005	28	4 months DCR	Ongoing, but not recruiting participants	May 20, 2015
II, single arm	Nintedanib	Tyrosine kinase inhibitor (anti-VEFR, FGFR, PDFGR)	A Phase II Trial of BIBF 1120 (Nintedanib) in Recurrent Malignant Pleural Mesothelioma	NCT02568449	55	PFS	Recruiting patients	October 2015
II, single arm	Brentuximab vedotin	Anti-CD30 monoclonal antibody	Phase II Trial of Adcetris (Brentuximab Vedotin) in CD30+ Malignant Mesothelioma	NCT03007030	50	DCR	Recruiting patients	April 5, 2017
I, II	YS110	Anti CD26 monoclonal antibody	Phase I/II Clinical Study of YS110 in Patients With Malignant Pleural Mesothelioma	NCT03177668	48	DLT DCR PFS OS RR	Recruiting	June 2017

AE, adverse events; *DCR*, disease control rate; *OS*, overall survival; *PFS*, progression-free survival; *RR*, response rate; *TTP*, time to progression; *DLT*, dose-limiting toxicity

Table 4. Clinical trials meeting primary endpoint in the evaluation of targeted therapy for pretreated malignant pleural mesothelioma

Agent	Trial	Population	Setting	Arms	*N*	Primary endpoint	ORR (%)	Median (ms)	HR (95%CI)
NGR-hTNF (modified tumor necrosis factor alpha)	Phase II [33, 34]	Short TFI (<median 4.8 ms)	2-line	NGR-hTNF + single agent CT; Single agent CT	198	OS*	–	–	0.69
Sorafenib (tyrosine kinase inhibitor)	Phase II [37]	Unselected	Pretreated	Sorafenib	53	6-ms PFS	–	5.1 (36% at 6-ms)	–
Tazemetostat (EZH2 inhibitor)	Phase II [51]	Inactive BAP1	Pretreated	Nivolumab	61	3-ms DCR	51% at 3 ms	–	–

CT, chemotherapy; *ms*, months; *N*, number; *ORR*, overall response rate; *OS*, overall survival; *PFS*, progression-free survival
*Results from subgroup analysis

Table 5. Key ongoing phase II and III clinical trials evaluating immunotherapy in pretreated malignant pleural mesothelioma

Phase	Study drug(s)	Drug(s) class	Clinical trial title	Clinical trial number	Estimated enrolment	Primary endpoint	Status	Start date
III, placebo controlled	Nivolumab vs placebo	Anti-PD1	CheckpOiNt Blockade For Inhibition of Relapsed Mesothelioma (CONFIRM): A Phase III Double-Blind, Placebo Controlled Trial to Evaluate the Efficacy of Nivolumab in Relapsed Mesothelioma	NCT03063450	336	OS	Recruiting patients	March 28, 2017
III, randomized	Pembrolizumab vs gemcitabine/ vinorelbine	Anti-PD1, nucleoside analogue, vinca alkaloid	A Multicentre Randomised Phase III Trial Comparing Pembrolizumab Versus Standard Chemotherapy for Advanced Pre-treated Malignant Pleural Mesothelioma	NCT02991482	142	PFS	Active, not recruiting	September 12, 2017
II, single arm	Durvalumab and tremelimumab	Anti-PD-L1, anti-CTLA4	A Phase 2 Study of Durvalumab in Combination With Tremelimumab in Malignant Pleural Mesothelioma	NCT03075527	40	RR	Recruiting patients	April 10, 2017
II, single arm	Tremelimumab and durvalumab	Anti-CTLA4, anti-PD-L1	A Single Arm, Phase II Clinical Study of Tremelimumab Combined With the Anti-PD-L1 MEDI4736 Monoclonal Antibody in Unresectable Malignant Mesothelioma Subjects: The NIBIT-MESO-1	NCT02588131	40	irRR	Unknown	October 2015
II, single arm	CRS-207 and pembrolizumab	Listeria monocytogenes–expressing mesothelin boost vaccines, anti-PD1	A Phase 2 Single-arm Study to Evaluate Safety and Efficacy of CRS-207 With Pembrolizumab in Adults With Previously-Treated Malignant Pleural Mesothelioma	NCT03175172	35	RR	Active, not recruiting	June 15, 2017

DCR, disease control rate; *CTLA-4*, cytotoxic lymphocyte antigen 4; *irRR*, immuno-RECIST response rate; *OS*, overall survival; *PD-1*, programmed death 1; *PD-L1*, programmed death-ligand 1; *PFS*, progression-free survival; *RR*, response rate; *TTP*, time to progression; *AE*, adverse events

Table 6. Results from clinical trials evaluating immunotherapy in pretreated malignant pleural mesothelioma

Agent	Trial	Population	Setting	Arms	N	Primary endpoint	ORR	Median (ms)	HR [95%CI]
Tremelimumab	Phase II [62]	PD-L1 unselected	2-line	Tremelimumab	29	ORR	7%	–	–
	DETERMINE [63] Phase IIb	PD-L1 unselected	2–3 lines	Tremelimumab; placebo	571	OS	–	7.7 7.3	0.92 [0.76 to 1.12]
Pembrolizumab	The Chicago [65] Phase II trial	PD-L1 unselected	2–3 lines	Pembrolizumab	35	ORR*	21%	–	–
Nivolumab	The NivoMes [66••]	PD-L1 unselected	Pretreated	Nivolumab	34	DCR	50% at 3 ms	–	–
	MAPS-2/IFTC1501 [67]	PD-L1 unselected	2–3 lines	Nivolumab + ipilimumab; nivolumab	54 54	3 ms DCR	50% 44.4%	–	–
Avelumab	JAVELIN Phase Ib [69]	PD-L1 unselected	Pretreated	Avelumab	53	ORR PFS	9.4%	17.1 weeks	–

ms, months; *N*, number; *ORR*, overall response rate; *OS*, overall survival; *PFS*, progression-free survival
*Results from interim analysis

immunomediated effects such as rash, pruritus, colitis, and diarrhea. Four patients had at least one grade 3–4 adverse event. Tremelimumab has been more extensively studied in a placebo-controlled phase IIb trial, the DETERMINE trial, which involved 571 MPM patients who had ECOG PS 0–1 and have received 1 or 2 previous therapies, including a first-line pemetrexed-based regimen [63]. Patients were randomized 2:1 and stratified according to risk, line of therapy, and anatomic site. Tremelimumab was administrated at 10 mg/kg IV every 4 weeks for 7 doses and then every 12 weeks until disease progression or unacceptable toxicity. Unfortunately, this study also did not meet its primary endpoint, since mOS was 7.7 months in the experimental arm in comparison with 7.3 months in the placebo group (HR=0.92; 95%CI 0.76–1.12, p=0.408). Based on these results, it seems reasonable that further development of tremelimumab in mesothelioma will be limited to combination therapies. Two phase II trials (NCT03075527, NCT02588131) are evaluating the combination of tremelimumab and durvalumab, an anti-PD-L1 monoclonal antibody, in pretreated MPM patients.

Anti-PD1 (nivolumab, pembrolizumab) or anti-PD-L1 (avelumab, atezolizumab, durvalumab) monoclonal antibodies block the inhibitory signaling between the tumor cell and T lymphocyte and thus prevent downregulation of T cell antitumor activity [60].

The phase Ib KEYNOTE-028 trial has evaluated pembrolizumab (10 mg/kg every 2 weeks for up to 2 years or until disease progression or unacceptable toxicity) in PD-L1–positive (expression in at least 1% of tumor cells by IHC) advanced solid tumors, including a mesothelioma cohort of pretreated patients [64••]. The primary endpoints were safety, tolerability, and objective response. Data from interim analysis of June 2016 are available. Eighty-four patients with mesothelioma were screened: 45% of them had PD-L1–positive tumors. Out of 25 patients treated with pembrolizumab, 16 (64%) had adverse events of which 5 (20%) were of grade 3. The most common side effects were fatigue (24%), nausea (24%), and arthralgia (20%). Five partial responses were observed for a RR of 20% and 13 patients (52%) obtained a stable disease; the median response duration was notable (12 months; 95%CI 3.7–not reached). Median OS was 18 months with 4 patients who had ongoing response for about 2 years.

The Chicago Phase II trial subsequently evaluated the activity of pembrolizumab in a larger PD-L1 unselected patient cohort with previously treated MPM [65]. The interim analysis of the first 35 patients enrolled (out 65 planned) showed a response rate of 21% and a disease control rate of 76%; mPFS and mOS were 6.2 and 11.9 months, respectively. Toxicity profile was in line to that expected except for fatal autoimmune hepatitis occurring in 3% of cases. Pembrolizumab will be compared with gemcitabine or vinorelbine in a phase III trial including pretreated MPM patients (NCT02991482) and will be evaluated, in a relapsed or refractory setting, in combination with CRS-207, a vaccine direct against mesothelin using an attenuated Listeria toxin (NCT03175172).

Encouraging results have been observed also with nivolumab for relapsed or refractory MPM. In the NivoMes phase II study, 50% 3-month DCR and a 3.6-month of mPFS were yielded in a cohort of 34 patients treated with nivolumab [66••]. The French Collaborative Thoracic Intergroup (IFCT) conducted a non-comparative randomized phase II study (MAPS2/IFCT1501) evaluating

nivolumab monotherapy (3 mg/kg every 2 weeks) and the combination of nivolumab with ipilimumab (1 mg/kg every 6 weeks) in patients with MPM who had disease progression after one or two lines of platinum-pemetrexed chemotherapy. The primary endpoint was 3-month DCR, targeting a DCR≥40% in each arm on the first 108 patients enrolled, to consider the study treatments as active. In both arms, the primary endpoint was met with a 3-month DCR of 50% with the combination therapy and 44.4% with nivolumab alone [67]. Updated data on survival analysis were presented at the ESMO 2017 Congress [68••]. After a median follow-up of 15 months, mOS was 13.6 months (95%CI 6.7–not reached) in the monotherapy arm, and was not even reached in the combination arm; mPFS was 5.6 months (95%CI 3.2–8.4) and 4.0 months (95%CI 2.8–5.7) with nivolumab plus ipilimumab and nivolumab alone, respectively. Immunohistochemistry performed in 99 patients revealed that just 41% expressed PD-L1 and only three patients expressed PD-L1 in more than 50% of tumor cells. However, PD-L1 expression was not significantly associated with OS or PFS. There were no unexpected toxicities. The adverse event rate was slightly superior in the combination arm compared to the monotherapy arm, but most side effects observed were of grades 1–2. These survival results support a recent decision by the US Food and Drug Administration to grant orphan drug status to the nivolumab alone and in combination with ipilimumab for relapsed or refractory MPM.

The efficacy of nivolumab monotherapy in relapsed MPM will have to be confirmed in an ongoing phase III placebo-controlled trial (NCT03063450).

Avelumab is under evaluation in a phase Ib trial conducted including previously treated MPM patients unselected for PD-L1 expression [69]. The primary endpoints were ORR and PFS. Until the interim analysis of October 2015, 53 patients had received avelumab at 10 mg/kg IV every 2 weeks. Overall, RR was 9.4%; according to PD-L1 status, the RR was 14.3% and 8% in PDL1-positive and PDL1-negative patients, respectively. The median PFS was longer in PD-L1–positive patients in comparison with the PD-L1–negative patients (17.1 weeks vs 7.4 weeks). Treatment-related adverse events occurred in 41 patients (77.4%); the most common (>10%) were infusion-related reaction (37.7%), fatigue (15.1%), chills (15.1%), and pyrexia (11.3%), all of grades 1–2.

Based on these preliminary results, targeting the PD-L1/PD1 axis seems to be a promising therapeutic strategy, but the efficacy should be confirmed in larger studies.

Conclusions

In current clinical practice, patients with MPM who maintain a good ECOG PS after failure of the first-line platinum-pemetrexed therapy can be retreated with the same front-line drugs or receive a second-line treatment with other cytotoxic drugs, such as gemcitabine and vinorelbine. However, the evidence supporting both therapeutic strategies is weak. All available studies have a single-arm design or a retrospective nature; thus, their external validity is hampered by a selection bias which makes results difficult, if not impossible, to understand. Considering also the poor efficacy of the available options, there is a need of randomized controlled trials in order to establish a new standard for the second-line chemotherapy of MPM. Moreover, the absence of a valid treatment

for refractory disease creates the issue about what should be used in the control arm, placebo or active therapy.

In the era of personalized medicine, there is a notable effort to identify mutations or translocations in MPM tumor which would drive tumor growth and might be exploited as a therapeutic target. Several targeted agents, used in other diseases, and novel mAb, direct to specific mesothelioma targets, have been evaluated as a potential second-line therapy. Unfortunately, this strategy successfully used in other types of cancer has never been replicated in MPM. A better understanding of MPM biology is strongly needed before new personalized or targeted therapies will be developed.

Immunotherapy appears to be the most promising among the emerging second-line treatments. Despite the limited experience derived from phase I/II clinical studies accumulating altogether more than 250 patients, preliminary results consistently suggest encouraging efficacy with acceptable toxicity, that should be confirmed in the ongoing phase III trials. The interesting activity of immunotherapy in MPM patients urges researchers to inquire into this innovative approach, also experimenting on combinations with other immunological or cytotoxic agents or exploring new predictive biomarkers of efficacy.

Compliance with Ethical Standards

Conflict of Interest

Vincenzo Di Noia, Emanuele Vita, Miriam Ferrara, Antonia Strippoli, Michele Basso, Giovanni Schinzari, Alessandra Cassano, Emilio Bria, Carlo Barone, and Ettore D'Argento declare they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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Papers of particular interest, published recently, have been highlighted as:

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