

# Novel systemic therapy against malignant pleural mesothelioma

Michael R. Mancuso, Joel W. Neal

Division of Oncology, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA

**Contributions:** (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Joel W. Neal. Division of Oncology, Department of Medicine, Stanford University School of Medicine, 875 Blake Wilbur Dr, RM 2220, Palo Alto, CA 94304, USA. Email: [jwneal@stanford.edu](mailto:jwneal@stanford.edu).

**Abstract:** Malignant pleural mesothelioma is an aggressive tumor of the pleura with an overall poor prognosis. Even with surgical resection, for which only a subset of patients are eligible, long term disease free survival is rare. Standard first-line systemic treatment consists of a platinum analog, an anti-metabolite, and sometimes anti-angiogenic therapy, but there is currently no well-established standard therapy for refractory or relapsed disease. This review focuses on efforts to develop improved systemic therapy for the treatment of malignant pleural mesothelioma (MPM) including cytotoxic systemic therapy, a variety of tyrosine kinase inhibitors and their downstream effector pathways, pharmacologic targeting of the epigenome, novel approaches to target proteins expressed on mesothelioma cells (such as mesothelin), arginine depletion therapy, and the emerging role of immunotherapy. Overall, these studies demonstrate the challenges of improving systemic therapy for MPM and highlight the need to develop therapeutic strategies to control this disease.

**Keywords:** Mesothelioma, chemotherapy, mesothelin, immunotherapy, clinical trials

Submitted Mar 28, 2017. Accepted for publication Apr 28, 2017.

doi: 10.21037/tlcr.2017.06.01

**View this article at:** <http://dx.doi.org/10.21037/tlcr.2017.06.01>

## Introduction

Malignant pleural mesothelioma (MPM) arises from the normal mesothelioma cells of the pleura and is generally associated with a poor prognosis, as many patients are diagnosed with advanced disease, and long-term disease free survival is rare even in the early stage setting. Physicians in the United States diagnose approximately 2,500 new cases per year (1). MPM affects more men than women with an incidence ratio of 3.8:1, and men have a lower overall 5-year survival (4.5%) compared to women (13.4%) (2). The median age of diagnosis in the United States is 72 years. Asbestos exposure was first identified as a cause of MPM in the 1960's, and it is estimated that up to 80% of cases of MPM are related to asbestos exposure with the onset of disease generally occurring 20–70 years after exposure through mechanisms of chronic inflammation (3–5). The incidence of MPM in the United States has stabilized over

the past few years likely due to decreased asbestos use since the 1970's (1); however, the incidence of MPM in developing countries is expected to increase and represents a substantial health and economic burden (6,7). Risk factors for mesothelioma also include environmental, occupational, and para-occupational exposure to asbestos and other mineral fibers such as erionite (8). Prior chest radiation therapy or occupational radiation also increases the risk for developing mesothelioma (9–15). Familial variants of mesothelioma exist as well: for example, two families with strong family history of mesothelioma without an associated history of exposure to asbestos or other mineral fibers were found to have familial mutations in *BRCA associated protein 1 (BAP1)*, a tumor suppressor gene, that either affects the gene's promoter or forms a premature stop codon (16). Somatic mutations of *BAP-1* have also been identified in 57–63% of cases (17).

Approximately 60% of patients with MPM present

with pleural effusion, dyspnea, and chest wall pain (18). The disease is typically locally invasive or even more extensive at presentation. The diagnosis of MPM requires adequate tissue in the context of appropriate clinical, radiographic, and surgical findings. Thoracoscopic biopsy is considered the gold standard diagnostic method and case series have reported diagnostic sensitivity to range from 94–98% (19–21). CT-guided needle biopsy is also commonly used and has a reported sensitivity of 83–88% (22–26). The International Mesothelioma Interest Group (IMIG) established diagnostic criteria based on cytology. These have low sensitivity ranging from 32–76%, because of the challenges in distinguishing a collection of benign mesothelial cells from invasive mesothelioma, but a high positive predictive value approaching 100% (27). Markers used to distinguish MPM from other types of pleural masses include cytokeratin 5/7, Wilm's Tumor 1 (*WT1*), D2-40 (podoplanin), and calretinin. Pathologists classify MPM tumors into three histological subtypes: epithelioid, sarcomatoid (which includes desmoplastic and lymphohistiocytic variants), or biphasic. The epithelioid histology occurs in 50–60% of patients and has a more favorable prognosis. The sarcomatoid histology comprises approximately 20% of cases and is associated a less favorable prognosis, as well as a lower chance of response to therapy.

Once the diagnosis is made, patients are staged based on the IMIG TNM staging system. All patients undergo CT imaging of the chest and abdomen, and ideally PET/CT scan is performed in patients being considered for surgery to evaluate for extrathoracic spread. Surgeons will often use MRI of the chest and/or abdomen for further evaluation when there is suspected diaphragmatic, spine, or vascular invasion. Additional procedures can be performed to exclude extra-pleural disease, including VATS to evaluate the contralateral pleura, and laparoscopy to rule out peritoneal spread prior to resection.

Management options presented to patients with MPM are determined based on the age and functional status of the patient and on the stage (including lymph node involvement), histology, and resectability of the disease. Younger patients with good performance status, epithelioid histology, and localized resectable disease can generally be offered multimodality therapy with systemic chemotherapy, surgical resection, and sometimes radiation therapy (28,29). Another article in this issue of *Translational Lung Cancer Research* discusses surgical options for MPM; however, we will briefly mention here that surgical options are generally limited to patients with the epithelioid subtype of MPM and

consist of pleurectomy/decortication (P/D) with mediastinal lymph node sampling or extrapleural pneumonectomy (EPP). Patients who will not benefit from P/D or EPP can be offered palliative systemic chemotherapy, depending on their functional status. While palliative radiation therapy can help improve symptoms from invasive disease, definitive radiation therapy has not been shown to be effective after an incomplete surgical resection and has elevated toxicity to the intact lung (30). While aggressive therapy is more effective in patients with early, limited MPM with epithelioid history (31,32), most patients present with higher stage disease or cannot tolerate extensive surgical resection due to advanced age and/or medical co-morbidities. These patients should be considered for systemic therapy. Even with treatment, MPM has a poor prognosis with median survival of approximately one-year and cure is very rare (33–35). The limited efficacy of therapy for MPM highlights the need to develop more effective therapies for MPM which is challenged by the heterogeneity of MPM (with three pathological subtypes), the relatively low incidence of the disease, and the degree of difficulty with assessment of response. Here, we review recent efforts to improve systemic therapies for MPM with ongoing trials listed in *Tables 1* and *2*.

### Cytotoxic chemotherapy for MPM

Surgical resection alone does not generally mitigate microscopic localized or metastatic disease, so adjuvant chemotherapy has been evaluated and shown to provide added benefit (28). Patients with medically inoperable mesothelioma are managed with observation, best supportive care, or systemic chemotherapy. Anti-metabolites such as pemetrexed, raltitrexed, and methotrexate, platinum analogs (cisplatin and carboplatin), gemcitabine, vinorelbine, and doxorubicin have activity in MPM with single-agent response rates of 7–20% (36). Anti-folate therapy with pemetrexed, combined with platinum therapy, with or without bevacizumab, is the current standard first-line systemic therapy for advanced or unresectable MPM (37,38).

The history leading to establishing anti-folate, platinum, and bevacizumab as front-line therapy spans decades. In the late 1980's and 1990's, randomized trials evaluated the efficacy of multiple single-agent chemotherapeutics including anthracyclines, topoisomerase inhibitors, taxanes, alkylating agents, and platinum analogues in MPM with low response rates of 0–13%, progression free survival of 2–5 months, and median overall survival ranging 5–8 months (39–43). Overall, single agent chemotherapy was persistently

**Table 1** Ongoing clinical trial in malignant pleural mesothelioma (as of April 20, 2017)

Trial category	Study drug(s)	Clinical trial title	Clinical trial number	Estimated enrollment	Phase	Date opened	Status
Cytotoxic chemotherapy	Pemetrexed	Randomized Phase II Study of Maintenance Pemetrexed Versus Observation for Patients With Malignant Pleural Mesothelioma Without Progression After First-Line Chemotherapy	NCT01085630	68	II	11-Mar-10	Ongoing, no longer recruiting patients
Targeting of Receptor Tyrosine kinases	Imatinib	A Phase II Study of the Combination of Gemcitabine and Imatinib Mesylate in Pemetrexed-pretreated Patients With Malignant Pleural Mesothelioma	NCT02303899	22	II	19-Nov-14	Ongoing, no longer recruiting patients
	Cetuximab	Phase II Study of Cetuximab Combined With Cisplatin or Carboplatin/Pemetrexed as First Line Treatment in Patients With Malignant Pleural Mesothelioma.	NCT00996567	22	II	15-Oct-09	Completed
	LY3023414	A Phase 1 First-in-Human Dose Study of LY3023414 in Patients With Advanced Cancer	NCT01655225	130	I	19-Jul-12	Recruiting patients
Anti-mesothelin	Amatuximab	A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of Amatuximab in Combination With Pemetrexed and Cisplatin in Subjects With Unresectable Malignant Pleural Mesothelioma.	NCT02357147	108	II	14-Jan-15	Ongoing, no longer recruiting patients
Anti-mesothelin-drug conjugate	Anetumab Ravtansine	A Randomized, Open-label, Active-controlled, Phase II Study of Intravenous Anetumab Ravtansine (BAY 94-9343) or Vinorelbine in Patients With Advanced or Metastatic Malignant Pleural Mesothelioma Overexpressing Mesothelin and Progressed on First Line Platinum/Pemetrexed-based Chemotherapy	NCT02610140	248	II	9-Nov-15	Ongoing, no longer recruiting patients
	BMS-986148	A Phase I/IIa Study of BMS-986148, a Mesothelin Directed Antibody Drug Conjugate, in Subjects With Select Advanced Solid Tumors	NCT02341625	407	I/IIa	14-Jan-15	Recruiting patients
	LMB-100	A Phase I Study of the Reduced Immunogenicity Mesothelin-Targeted Immunotoxin LMB-100 in Patients With Malignant Mesothelioma	NCT02798536	30	I	10-Jun-16	Recruiting patients
EZH2 inhibitor	Tazemetostat	A Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects With Relapsed or Refractory Malignant Mesothelioma With BAP1 Loss of Function	NCT02860286	67	II	27-Jul-16	Recruiting patients
Arginine depletion	ADI-PEG 20	Randomized, Double-Blind, Phase 2/3 Study in Subjects With Malignant Pleural Mesothelioma With Low Argininosuccinate Synthetase 1 Expression to Assess ADI-PEG 20 With Pemetrexed and Cisplatin (ATOMIC-Meso Phase 2/3 Study)	NCT02709512	386	II/III	5-Mar-16	Recruiting patients
Heat-shock protein inhibitor	Ganetespib	A Phase I/II Study of First Line Ganetespib With Platinum, in Patients With Malignant Pleural Mesothelioma	NCT01590160	27	I/II	30-Apr-12	Ongoing, no longer recruiting patients

**Table 2** Ongoing immunotherapy clinical trial in malignant pleural mesothelioma (as of April 20, 2017)

Trial category	Study drug(s)	Clinical trial title	Clinical trial number	Estimated enrollment	Phase	Date opened	Status
Anti-PD-L1 therapy	Durvalumab	Open Label, Phase II Study of Anti-Programmed Death-Ligand 1 Antibody, Durvalumab (MEDI4736), in Combination With Chemotherapy for the First-Line Treatment of Unresectable Mesothelioma	NCT02899195	55	II	8-Sep-16	Pending
	Durvalumab	A Phase 2 Study of Durvalumab in Combination With Tremelimumab in Malignant Pleural Mesothelioma	NCT03075527	40	II	2-Mar-17	Recruiting patients
	Durvalumab	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	II	26-Oct-15	Recruiting patients
	Durvalumab	Window of Opportunity Phase II Study Of MEDI4736 or MEDI4736 + Tremelimumab In Surgically Resectable Malignant Pleural Mesothelioma	NCT02592551	20	II	19-Oct-15	Recruiting patients
Anti-PD-1 therapy	Pembrolizumab	A Phase II Study of the Anti-PD-1 Antibody Pembrolizumab in Patients With Malignant Mesothelioma	NCT02399371	65	II	13-Mar-15	Recruiting patients
	Pembrolizumab	A Pilot Window-of-opportunity Study of the Anti-PD-1 Antibody Pembrolizumab in Patients With Resectable Malignant Pleural Mesothelioma	NCT02707666	15	II	29-Feb-16	Recruiting patients
	Pembrolizumab	A Multicentre Randomised Phase III Trial Comparing Pembrolizumab Versus Standard Chemotherapy for Advanced Pre-treated Malignant Pleural Mesothelioma	NCT02991482	142	II	9-Dec-16	Pending
	Nivolumab	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	III	10-Feb-17	Recruiting patients
	Nivolumab	A Randomized Phase II Study Evaluating Efficacy and Safety of 2nd or 3rd Line Treatment by Nivolumab Monotherapy or Nivolumab Plus Ipilimumab, for Unresectable Malignant Pleural Mesothelioma (MPM) Patients	NCT02716272	125	II	9-Mar-16	Ongoing, no longer recruiting patients
Anti-PD-1 and anti-CTLA4	Nivolumab and Ipilimumab	A Phase III, Randomized, Open Label Trial of Nivolumab in Combination With Ipilimumab Versus Pemetrexed With Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma	NCT02899299	600	III	31-Aug-16	Recruiting patients
	Tremelimumab and Durvalumab	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	II	26-Oct-15	Recruiting patients

been found to have a modest response in patients with mesothelioma, with slightly better responses of around 23% (95% CI: 19.7–26.8) observed with cisplatin across many clinical trials (36,44).

### ***Combination of pemetrexed added to platinum therapy***

In 2003, Vogelzang *et al.* published the landmark phase III EMPHACIS trial reporting that addition of pemetrexed to cisplatin improved outcomes for patients with MPM (37). Chemotherapy naïve patients who were not eligible for curative surgery were randomized to 500 mg/m<sup>2</sup> pemetrexed and 75 mg/m<sup>2</sup> of cisplatin (n=226) or cisplatin alone (n=222) every 21 days. The addition of pemetrexed to cisplatin improved the response rate from 16.7–41.3% compared to cisplatin alone. The median time to progression was significantly longer in the pemetrexed plus cisplatin group at 5.7 months compared to 3.9 months in the cisplatin alone group (P=0.001). The median overall survival in the pemetrexed group was 12.1 months compared to 9.3 months in the cisplatin alone group (P=0.02). Similarly, van Meerbeeck *et al.* conducted a European randomized phase III clinical trial (EORTC) with 250 patients randomized to cisplatin 80 mg/m<sup>2</sup> either alone or with raltitrexed 3 mg/m<sup>2</sup> (45). The response rate was 13.6% in the cisplatin alone arm and 23.6% in the cisplatin plus raltitrexed arm (P=0.056). Similar to the EMPHACIS trial (37), the addition of this anti-folate therapy to cisplatin improved median overall survival by three months from 8.8 months (95% CI: 7.8–10.8) to 11.4 months (95% CI: 10.1–15.0).

In clinical practice, carboplatin is often substituted for cisplatin due to its reduced risk of toxicity (46). Phase II data demonstrated the efficacy of pemetrexed (500 mg/m<sup>2</sup>) plus carboplatin AUC 5 in MPM (47–49). Santoro *et al.* reported a slightly lower response rate of 21.7% (95% CI: 18.8–24.8) for carboplatin-based chemotherapy compared to a response rate of 26.3% (95% CI: 23.2–29.6) for cisplatin-based chemotherapy when combined with pemetrexed. However, this study observed that time to progression and 12-month survival were essentially equivalent with both regimens (50).

### ***Gemcitabine with platinum therapy***

Gemcitabine appears to be an active drug in MPM as well. A retrospective series of 81 MPM patients treated first-line with a platinum analog plus gemcitabine (n=40) or pemetrexed (n=41) showed that the efficacy of gemcitabine

and pemetrexed platinum doublets are similar (51). Byrne *et al.* observed partial responses in 10 out of 21 (47.5%, 95% CI: 26.2–69) patients with MPM treated with cisplatin 100 mg/m<sup>2</sup> on day 1 and gemcitabine 1,000 mg/m<sup>2</sup> on days 1, 8, 15 of a 28-day cycle for six cycles (52). This same regimen was further evaluated in a multicenter phase II study with 52 patients with MPM of which 17 (33%, 95% CI: 20–46) had a partial response (53). Kalmadi *et al.* reported a 12% response rate (95% CI: 5–24%) with cisplatin divided into weekly doses at 30 mg/m<sup>2</sup> to reduce toxicity (54). Ak *et al.* found no difference in survival between patients who received platinum therapy with pemetrexed compared to those who received platinum therapy with gemcitabine (55). Carboplatin with gemcitabine has also been tested in MPM with a response rate of 26% (95% CI: 15–40%) with acceptable toxicity (56). Overall, gemcitabine combined with platinum agents appears to be an active regimen in MPM; however, there is heterogeneity between trials with response rates ranging 12–48% and median survival ranging from 9.5 to 12 months (52–54,57,58).

### ***Vinorelbine***

Single agent therapy with the semisynthetic vinca alkaloid vinorelbine has a response rate of 24% with low toxicity (59). In the front line setting, vinorelbine combined with oxaliplatin has a 23% response rate (95% CI: 9–44%) (60). In the relapsed setting, patients who have had a prior chemotherapy demonstrated a 16% response rate to vinorelbine 30 mg/m<sup>2</sup> for 6 weeks (61). A phase III trial randomized 409 patients to receive active symptom control with or without chemotherapy which consisted of either four cycles of mitomycin C 6 mg/m<sup>2</sup>, vinblastine 6 mg/m<sup>2</sup>, and cisplatin 50 mg/m<sup>2</sup> every 21 days, or 12 weekly doses of vinorelbine 30 mg/m<sup>2</sup> (62). Overall, there was a trend towards improvement in survival with vinorelbine; however, the study was underpowered due to poor accrual in the setting of platinum and pemetrexed becoming preferred first-line therapy for MPM (37,62–64).

### ***2<sup>nd</sup> line and salvage therapy***

Generally, patients of good performance status who relapse after frontline therapy can be considered for retreatment with the initial regimen depending on the interval of disease control, or second line therapy with gemcitabine or vinorelbine based on the evidence discussed above. Patients in the EMPHACIS trial who received post-study

chemotherapy had a statistically prolonged survival with an adjusted hazard ratio of 0.56 (CI: 0.44–0.72), demonstrating benefit of additional systemic therapy after first line treatment (65). Prior to cisplatin and pemetrexed becoming the first-line standard of care, Jassem *et al.* showed that pemetrexed increased progression free survival in previously treated, pemetrexed-naïve patients (66). Patients with relapsed disease after pemetrexed-based first-line therapy can be considered for retreatment with pemetrexed based chemotherapy if disease control is achieved for more than 12 months after administration of first line therapy (67). There are ongoing investigations regarding the role of maintenance pemetrexed therapy, because this approach has a superior overall survival in patients with non-small cell lung cancer (68,69). A case report demonstrated that pemetrexed maintenance therapy is feasible in MPM (70), and a clinical trial investigating the efficacy of pemetrexed maintenance is currently ongoing (clinicaltrials.gov NCT01085630).

### Anti-angiogenic therapy

Tumor growth requires angiogenesis, the growth of new blood vessels into a tumor to supply oxygen and other nutrients (71). Several anti-angiogenesis strategies have been tested clinically in MPM. Thalidomide was first shown to inhibit angiogenesis in a corneal micro-pocket assay (72). Based on these, and other findings (73), clinical investigators have tested thalidomide in patients with MPM. The randomized phase III NVALT 5 trial compared thalidomide maintenance therapy to best supportive care after at least four cycles of pemetrexed with platinum therapy. Unfortunately, no benefit was noted in time to progression (3.6 months in the thalidomide group versus 3.5 months in the best supportive care group) with the addition of thalidomide maintenance to first-line chemotherapy (74).

The Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) was initiated as a phase II trial to determine if adding bevacizumab, a monoclonal antibody against the endothelial cell mitogen Vascular Endothelial Growth Factor-A (VEGF-A), to cisplatin and pemetrexed provided clinical benefit. This study met the primary outcome with 27 patients out of 47 patients achieving disease control at 6 months without unexpected toxicity signals. The study then expanded to a randomized, controlled, open-label, phase III trial with 448 patients. The addition of bevacizumab to cisplatin and pemetrexed significantly increased overall survival to 18.8 months in patients who

received bevacizumab, cisplatin, and pemetrexed (n=223) *vs.* 16.1 months in patients who received cisplatin and pemetrexed (n=225) (38). Based on this trial, consideration should be given to bevacizumab in front-line therapy with pemetrexed and cisplatin or carboplatin in clinical practice.

Clinical trials have also investigated the efficacy of small molecule inhibitors of angiogenesis. Nintedanib is an intracellular inhibitor of tyrosine kinase receptor signaling with specificity for VEGFR1-3, platelet derived growth factor receptor (PDGFR)- $\alpha$  and - $\beta$ , and fibroblast growth factor receptor (FGFR)1-3. Grosso *et al.* presented positive data at the 17<sup>th</sup> IASLC World Conference on Lung Cancer reporting the addition of nintedanib versus placebo to chemotherapy with cisplatin and pemetrexed increased progression free survival (9.4 *vs.* 5.7 months, P=0.0174). There was also a preliminary trend towards improved overall survival (18.3 *vs.* 14.5 months, P=0.4132) but further investigation is needed to statistically confirm this survival benefit (75). Cediranib is a potent small molecule inhibitor of VEGFR1-3, c-Kit, and PDGFR- $\beta$  signaling (76,77). Patients with MPM who had previously been treated with platinum containing therapy demonstrated a 9–10% response rate to therapy with cediranib 45 mg po daily (78,79). Tsao *et al.* reported the phase I portion of the SWOG 0905 evaluating cediranib combined with standard of care platinum and pemetrexed therapy followed by cediranib maintenance therapy in chemotherapy naïve patients with unresectable MPM (80). Patients who received 6 cycles of cediranib in combination with platinum and pemetrexed therapy followed by cediranib maintenance therapy (20 mg daily) had a median PFS of 13 months and OS of 16 months, which is better than expected from historical controls (37,80).

Sunitinib, which targets VEGFR1-3, demonstrated a response in only one treatment naïve patient out of 35 total enrolled, in a study including MPM patients with and without prior therapy (81). Similarly, vatalanib demonstrated a low response rate in a phase II study (82). Sorafenib, a potent inhibitor of the RAS/MEK pathway which also targeted VEGFR and cKIT, had a response rate of 6% at a dose of 400 mg po BID in patients with unresectable MPM with or without prior therapy (83). Another phase II trial reported that 36% patients treated with sorafenib 400 mg po BID were progression free at 6 months (84). While these findings are comparable to other small molecular inhibitors of angiogenesis, additional studies are needed to determine if this translates into clinical benefit. As discussed below, pre-clinical studies demonstrate efficacy of sorafenib

combined with everolimus in mesothelioma xenografts (85), which provides a rationale for combination studies with multiple agents.

### PDGFR inhibitors

Normal mesothelial cells express PDGFR- $\alpha$  while mesothelioma tumors express both PDGF-AA and PDGF-BB ligands as well as PDGFR- $\alpha$  and PDGFR- $\beta$  (86-88). While the staining pattern of PDGFR- $\beta$  immunoreactivity in frozen sections of MPM are consistent with MPM tumor cell expression of PDGFR- $\beta$ , the function of PDGFR- $\beta$  within tumor cells, as opposed to the associated stroma, has not been well described. The finding of high PDGF-AA and PDGF-BB ligands and PDGFR- $\alpha$  and PDGFR- $\beta$  expression in MPM tumors led to the hypothesis that targeting PDGFR signaling could provide clinical benefit. Several receptor tyrosine kinase inhibitors active against PDGF/PDGFR signaling have been developed, including imatinib and vatalanib (described above). Imatinib is best characterized for its efficacy in chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (89,90). While pre-clinical models showed that imatinib caused apoptosis in MPM cells lines and synergizes with gemcitabine (91), several phase I/II trials did not show efficacy imatinib monotherapy in patients with MPM. In a phase II study using imatinib at a dose of 200 mg BID, none of the 11 patients had a response (92) and, in another phase II study, none of the 17 MPM patients had a response to imatinib at a dose of 600 mg BID (93). Similarly, negative results were observed in a study in the Netherlands where 25 patients were treated with imatinib with doses ranging from 400 to 800 mg po BID without clinical response (94). The results of these three clinical trials show that single agent imatinib does not appear to offer clinical benefit to patients with MPM.

Several pre-clinical models indicated that imatinib reduces the interstitial pressure of tumor tissue and therefore could perhaps enhance delivery of other therapeutics (95). Further, *in vitro* studies demonstrate synergy between imatinib and gemcitabine or pemetrexed (96). With this rationale, a phase I study evaluated imatinib in combination with cisplatin and pemetrexed in 17 patients with MPM who had never received chemotherapy (97). Tsao *et al.* tested a regimen of cisplatin 75 mg/m<sup>2</sup>, pemetrexed 500 mg/m<sup>2</sup>, and imatinib mesylate 600 mg po BID; however, the regimen was only tolerable in good performance status patients. Seven out of the 17 patients received two cycles of

therapy or less. By RECIST criteria, 1 patient had a partial response, and 3 had a minor response. Six patients were able to complete 6 cycles of chemotherapy and demonstrated a median progression free survival of 9.6 months and overall survival of 22.4 months. While this is higher compared to historical controls, this study was not designed to determine if the addition of imatinib to cisplatin and pemetrexed provided clinical benefit (97). In the setting of refractory MPM, a phase I study combined imatinib mesylate with gemcitabine where 1 patient out of 5 had a partial response (98). A phase II study is currently underway evaluating efficacy of imatinib in combination with gemcitabine in patients with MPM who had previously been treated (clinicaltrials.gov NCT02303899).

### MET/HGF inhibitors

The mesenchymal-epidermal transition factor (*MET*) proto-oncogene encodes a receptor tyrosine kinase that, upon being bound by the ligand Hepatocyte Growth Factor (HGF), transduces signals from the extracellular matrix into the cytoplasm. This activates several signaling cascades including the RAS-ERK, PI3 kinase-AKT, or PLC gamma-PKC, which regulate physiological processes including proliferation, migration, and survival. Over-expression, amplification, and mutation in *Met* have been described in MPM cell lines and inhibition of MET reduces proliferation of MPM cells *in vitro* (99). However, there currently are no studies, to our knowledge, evaluating efficacy of MET inhibitors in MPM.

### EGFR inhibitors

Prior studies reports that the percentage of MPM tumors that express epidermal growth factor receptor (EGFR) ranges from 32–97% (100-106). Preclinical studies demonstrate sensitivity of MPM cell lines to EGFR inhibitors (107). These findings have led to the hypothesis that targeting EGFR could be beneficial. There are two approaches to target EGFR which have been shown to be effective in patients with EGFR-mutated NSCLC, head and neck cancer, and RAS wild-type colon cancer. Small molecules, such as gefitinib and erlotinib, cross the plasma membrane of the targeted cell and bind to the intracellular domain of EGFR and inhibit EGFR signaling. Monoclonal antibodies, such as cetuximab, bind to the extracellular domain of EGFR and inhibit downstream signaling. Unfortunately, there is little evidence of efficacy from

targeting EGFR in MPM. In a phase II study, none of the 63 MPM patients responded to single agent erlotinib in the front line setting despite high expression of EGFR (103). In a phase II trial evaluating single-agent gefitinib in the front line setting, only 2 out of 43 patients responded to therapy and thus the investigators of this study concluded that gefitinib is not active in MPM (104). A clinical trial evaluating cetuximab in combination with pemetrexed and either cisplatin or carboplatin in the front line setting is ongoing (clinicaltrials.gov NCT00996567).

### PI3K/AKT/mTOR pathway inhibitors

Phosphatidylinositol-4,5-bisphosphate 3-kinases (PI3K) s are composed of an 85 kDa regulatory subunit and a 110 kDa catalytic subunit that phosphorylates phosphatidyl inositol as a mechanism of intracellular signal transduction through mammalian target of rapamycin (mTOR)/AKT/ERK pathways regulating proliferation, differentiation, motility, and survival (108). Mutations in genes involved in PI3K signaling have been identified in MPM and are thought to contribute to the pathogenesis of MPM (109). Everolimus inhibits PI3K through binding mTOR and is FDA approved for metastatic breast cancer, renal cell carcinoma, subependymal giant cell astrocytoma, GI and lung neuroendocrine tumors, and for prevention of graft failure (110–113). Unfortunately, patients with MPM who had progressed after first line therapy did not respond to everolimus in a phase II study (114). Preclinical models have demonstrated promising efficacy in MPM patient derived xenograft models with a combination of everolimus and sorafenib (85) suggesting that the combination of receptor tyrosine kinase and mTOR inhibition could be effective. Other inhibitors of PI3K/mTOR are currently in clinical trials. A first in-human study is underway with the PI3K/mTOR inhibitor LY3023414, a small molecule that functions as a selective ATP-competitive inhibitor of PI3K $\alpha$  and mTOR, DNA-PK in *in vitro* studies (clinicaltrials.gov NCT01655225). A phase I study evaluating safety and tolerability of apitolisib, a potent small molecule inhibitor of PI3K and mTOR, reported a partial response in 2 out of 26 MPM patients (115). Recently, *in vitro* studies demonstrated that targeting MET and PI3Ks provides synergistic inhibition of MPM cell proliferation and migration, induction of apoptosis, and reduction in growth of an MPM patient derived xenograft mouse model (116), which provides a rationale for combinatorial therapy.

### Targeting epigenetic regulators

A comprehensive genomic analysis identified mutations in *BAP1* in 23% of MPM samples (117). Similarly, somatic mutations in *BAP1* have been reported in approximately 20% of cases of MPM (118) and linkage analysis demonstrated that germ-line mutations in *BAP1* are associated with familial MPM (16). The *BAP1* gene encodes a ubiquitin hydrolase that functions as a catalytic unit of the polycomb repressive deubiquitinase complex crucial for regulating gene expression and facilitating DNA repair (119,120). The recurrent mutations in *BAP1* prompted investigation into the use of histone deacetylase inhibitors in MPM. A phase I trial reported a partial response in 2/13 patients with MPM (121). The phase III clinical trial VANTAGE-014 sought to determine if vorinostat could improve overall survival as a 2<sup>nd</sup> or 3<sup>rd</sup>-line agent. On this trial, 661 patients were enrolled across 90 international centers, and randomized in a double blind fashion to receive either vorinostat 300 mg or matching placebo twice daily on days 1, 2, 3, 8, 9, 10, 15, 16, and 17 of a 21-day cycle. The study found that median overall survival for patients who received vorinostat was 30.7 weeks (95% CI: 26.7–36.1) vs. 27.1 weeks (23.1–31.9) for placebo (hazard ratio 0.98, 95% CI: 0.83–1.17, P=0.86), demonstrating that vorinostat given as a second-line or third-line therapy did not improve overall survival (122). Similar clinical findings were noted for another histone deacetylase inhibitor, belinostat (123). While these clinical studies demonstrate lack of benefit after pharmacologic inhibition of histone deacetylase to target epigenetic regulation in MPM, a preclinical study identified synthetic lethality with pharmacologic inhibition of enhancer of zeste 2 polycomb repressive complex 2 subunit (*Ezh2*) in MPM cells lacking *Bap1* (124). A phase II study evaluating efficacy of the EZH2 inhibitor tazemetostat in patients with both *Bap1*-deficient and wild-type relapsed or refractory MPM is currently ongoing (clinicaltrials.gov NCT02860286).

### Focal adhesion kinase (FAK) inhibitors

NF-2 encodes the tumor suppressor Moesin-ezrin-radixin-like protein (Merlin), a protein that functions as a membrane-cytoskeleton scaffold. Merlin inhibits FAK, a ubiquitously expressed intracellular protein localized to areas where the cell membrane attaches to the extracellular matrix. FAK integrates signals from integrins, which are cell surface glycoproteins that interact with the

extracellular matrix, into downstream effector pathways to regulate cell migration, adhesion, invasion, and self-renewal (125). Consequently, loss of *NF-2*/Merlin leads to tumorigenesis through dysregulation of migration which leads to an invasive phenotype. Germ-line loss of function mutations or deletions of *NF2* cause neurofibromatosis, a disorder characterized by development of schwannomas, meningiomas, and ependymomas. Somatic mutations leading to loss of *NF2* have been described in numerous cancers, including MPM. The recently published comprehensive genomic profiling of MPM identified mutations in *NF-2* in 19% of cases (117).

Defactinib is a second generation small molecule inhibitor of FAK. Pre-clinical models demonstrated that maintenance therapy with defactinib delayed tumor regrowth in MPM patient derived xenograft models (126). In a phase I study, one patient with MPM was reported to have radiographic stable disease while on defactinib for 24 weeks at a dose of 400 mg (127). Interestingly, another phase I study with a different FAK inhibitor, GSK2256098, reported that MPM patients with documented loss of Merlin had increased median PFS at 23.4 weeks (n=14) compared to MPM patients with preserved Merlin expression who had median PFS at 11.4 weeks (n=9) (128). This study was not designed to show a statistically significant difference in PFS but suggested that further studies could consider patient stratification based on *NF2* mutations status or levels of Merlin expression. Overall, these studies provided a rationale for a phase IIb study to evaluate defactinib as maintenance therapy in MPM patients after first line therapy with pemetrexed and a platinum agent. Unfortunately, this phase II study has been terminated after enrollment of 344 patients due to lack of observed efficacy (COMMAND, clinicaltrials.gov NCT01870609).

### Hsp90 inhibition

Heat shock proteins (HSPs) constitute a large family of proteins involved in protein folding and maturation. The major groups of HSPs are classified based on molecular weight of which HSP90 has been implicated in multiple malignancy types (129). Targeting HSP90 is an attractive therapeutic strategy as HSP90 functions to stabilize and fold multiple client proteins involved in cancer cell signaling such as EGFR, IGF-1R, CDK4, AKT, ErbB2, c-Met, BCR-ABL, RET, androgen receptors, Fms-like tyrosine kinase 3 (FLT3), BRAF, NF- $\kappa$ B, Raf-1, HER2/Neu, NPM-

ALK, p53, neuronal nitric oxide synthase (nNOS), and HIF-1 $\alpha$  (129). Ganetespib binds to and inhibits HSP90, resulting in the proteasomal degradation of oncogenic client proteins (130). A phase I/II clinical trial (MESO-02, clinicaltrials.gov NCT01590160) evaluating ganetespib with platinum in the front-line setting has completed accrual and results are pending.

### Proteasome inhibition

The potent proteasome 20S inhibitor bortezomib is approved for use in multiple myeloma (131). The mechanism through which bortezomib inhibition of the proteasome leads to cancer cell death is not fully understood but is thought that disruption of the single proteasome target affects multiple signaling pathways. Bortezomib induces cell cycle arrest and is synergistic with cisplatin in MPM cell line *in vitro* (132). In the second line setting, only 1 out of 23 patients treated with bortezomib and cisplatin demonstrated a partial response in a single arm phase II study (133). In the front-line setting, the response rate to bortezomib combined with cisplatin in MPM was reported at 28.4% (95% CI: 18.9–39.5%) with a median overall survival of 13.5 months (85% CI: 10.5–15 months). Unfortunately, the progression free survival at 18 weeks was 53% (80% CI: 42–64%) which was below the threshold to predict success of cisplatin and bortezomib in a phase III study and there are no further plans to study bortezomib with cisplatin (134).

### Immuno-targeting of mesothelin

Chang *et al.* first identified mesothelin as the antigen of the K1 monoclonal antibody generated from mice immunized with an ovarian cancer cell line (135). The *mesothelin* gene encodes a 69 kD protein which is cleaved into a 40 kD and 32 kD fragment. The 40 kD fragment is anchored to the surface of mesothelial cells lining the pleura by a GPI-linked membrane-bound protein. MPM expresses mesothelin at high levels since this malignancy arise from normal mesothelial cells. The physiologic function of mesothelin is unknown and mice lacking mesothelin do not have a phenotype (136). The high expression of mesothelin on MPM compared to normal tissue implies that mesothelin could be an effective target for immune guided therapies. Against this background, multiple anti-mesothelin therapeutic strategies have been developed including the monoclonal antibody amatuximab, an antibody-drug conjugates with the fully human anti-mesothelin antibody

intetumumab (NFT), and recombinant immunotoxins.

### *Amatuximab*

The mouse-human chimeric IgG1k monoclonal antibody amatuximab has a binding affinity of 1.5 nM for human mesothelin (137). Two phase I clinical trials identified a maximum tolerated dose of 200 mg/m<sup>2</sup>; however, no responses were seen in patients with MPM who received this agent (138,139). In a phase II study, amatuximab combined with pemetrexed and cisplatin in patients with unresectable epithelioid MPM did not show overlapping toxicities (140). The addition of amatuximab to pemetrexed and cisplatin did not prolong PFS longer than historical controls; however, median OS was 14.8 months compared to the historical control of 13.3 months for pemetrexed and cisplatin along. A phase II double blind placebo controlled study in six centers is ongoing (clinicaltrials.gov NCT02357147).

### *Antibody-drug conjugates*

There are currently three different antibody-drug conjugates targeting mesothelin expressing cells in clinical trials (141). The concept of a “magic bullet” delivering a potent chemotherapeutic to cancer cells and not normal healthy cells was first proposed over a century ago (142). Today, standard of care oncology practice utilizes antibody-drug conjugates with the approval of trastuzumab-emtansine (TDM1) (143) and brentuxumab vedotin (144-146). Antibody drug conjugates seek to utilize the specificity of antibody affinity to deliver highly potent cytotoxic agents specifically to cancer cells. While conceptually simple, the effectiveness of an antibody-drug conjugate depends on the effectiveness of the antibody, drug, and the linker fastening the drug to the antibody. After systemic administration, the antibody-drug conjugate binds the targeted epitope on the surface of the cancer cell which then internalizes the antibody-drug conjugate by receptor mediated endocytosis (147). Once internalized, the cytotoxic drug is released from the antibody through either hydrolysis, enzymatic cleavage, or degradation of the antibody depending on the linker used.

Anetumab raptansine is currently undergoing clinical testing in MPM. Phage library display panning led to the identification of Fab MF-T which binds mesothelin with 10 nM affinity (148). The conjugation of MF-T to the maytansinoid tubulin inhibitor DM4 through a hindered disulfide linker generated the antibody-drug conjugate

anetumab raptansine (BAY94-9343) (148). The uptake of the DM4 toxin causes inhibition of mitosis through targeting microtubule polymerization (149). Further, neighboring cells are also affected through a phenomenon known as “bystander cytotoxicity” where active drug metabolites diffuse into neighboring cells (150). A phase I study of intravenously infused anetumab raptansine every 3 weeks in 147 cancer patients identified a maximum tolerated dose of 6.5 mg/kg. The investigators identified keratopathy, asymptomatic increase in serum aminotransferase levels, and gastrointestinal upset as adverse events. In a subset of patients with MPM treated with anetumab raptansine at the maximum tolerated dose of 6.5 mg/kg i.v. every 3 weeks (n=16), 31% of patients had a partial response and 44% of patients has stable disease for an overall disease control rate of 75% (151) (clinicaltrials.gov NCT01439152). Encouraged by these results, these investigators are currently performing a phase II trial in 2<sup>nd</sup>-line metastatic pleural mesothelioma (clinicaltrials.gov NCT02610140).

Using antibody-drug conjugate technology, the humanized mouse anti-mesothelin antibody 7D9 was linked to monomethyl auristatin E via a lysosomal protease-cleavable valine-citrulline dipeptide linker, and has demonstrated promising activity in preclinical models (152). A phase Ia/II study of a mesothelin-directed antibody drug conjugate with an undisclosed cytotoxic drug (BMS-986148) was initiated in patients with advanced solid tumors, including mesothelioma, and this study is currently recruiting patients for enrollment (clinicaltrials.gov NCT02341625).

### *Recombinant immunotoxins*

Two novel agents, SS1P and RG7787 (LMB-100), link anti-mesothelin moieties to portions of *Pseudomonas* endotoxin A (141). These agents have potent efficacy *in vitro* (153) and the anti-tumor effect is enhanced in mouse models with prior administration of paclitaxel which is thought to decrease interstitial tumor pressure and increases tumor uptake of recombinant immunotoxin (154-156). Phase I studies have shown that both bolus and infusional doses of SS1P were complicated by generation of neutralizing antibodies to the *pseudomonas* endotoxin (157,158). Hassan *et al.* markedly delayed the development of these neutralizing antibodies by administering pentostatin and cyclophosphamide before and during administration of SS1P to deplete T and B lymphocytes. Of the 10 patients with chemotherapy-refractory MPM, 3 had major tumor regression and antibody formation was markedly delayed,

allowing for more cycles to be given (159). Hollevoet *et al.* de-immunized the effector moiety of the pseudomonas endotoxin A and fused it with a mesothelin targeting moiety to generate RG7787 (156). This recombinant immunotoxin has activity in MPM patient derived xenograft models (160). RG7787 was renamed LMB-100 and there is currently a phase I study accruing patients to evaluate the maximum tolerated dose of RG7787/LMB-100 in patients with MPM (clinicaltrials.gov NCT02798536).

### Arginine depletion

Preclinical models demonstrated that arginine deprivation is synthetically lethal in MPM cells that do not express argininosuccinate synthetase 1 (ASS1) (161). Approximately 60% of MPM tumors have loss of ASS1. Ubiquitous expression of ASS1 in normal cells offers a wide therapeutic window for arginine depletion therapy as the toxicity to normal cells is low. A phase II multicenter study compared administration of pegylated arginine deiminase (Adi-PEG 20, 36.8 mg/m<sup>2</sup> i.m. weekly) in addition to best supportive care to best supportive care alone in patients with ASS1 negative MPM (162). The study enrolled 201 patients, of which 97 were found to have ASS1 deficient disease as defined by >50% low expressing cells as visualized by an anti-ASS1 antibody. As an aside, the investigators were unable to determine the ASS1 status of 21 patients and the remaining 83 ASS1 positive patients were analyzed for overall survival. Szlosarek *et al.* reported a PFS hazard ratio of 0.56 (95% CI: 0.33–0.96) with a median PFS of 3.2 months in the Adi-PEG 20 group compared to 2.0 months in the best supportive care group alone (P=0.03) (162). The authors observed nonfebrile neutropenia, gastrointestinal toxicity, and fatigue as the most common adverse events. A phase I dose escalation study which combined Adi-PEG 20 with cisplatin and pemetrexed provided a signal of efficacy with a 78% response rate (7 out of 9 patients) (163). These findings are consistent with demonstrated efficacy of arginine depletion therapy in other malignancies (164–167). A phase 2/3 study is currently recruiting patients with MPM with low ASS1 expression to evaluate the efficacy of Adi PEG 20 in combination with pemetrexed and cisplatin (clinicaltrials.gov NCT02709512).

### Immunotherapy

The advances in immunotherapeutic approaches for MPM are reviewed in more detail elsewhere in this issue of

Translational Lung Cancer Research. However, highlights of recent immunotherapy trials will be presented here. The immune compartment has proven to be a key component of the tumor microenvironments role in tumor initiation, progression, and response to therapy (168). Targeting molecular regulators of immune function, namely cytotoxic lymphocyte antigen 4 (CTLA4) and Programmed Death-1/Programmed Death-Ligand 1 (PD/PD-L1) signaling axis have emerged as effective therapeutic strategies in multiple cancers (169). Recent efforts have focused on determining if MPM is responsive to immunotherapy. MPM has a high variability of lymphocytic infiltration, but prolonged survival is associated with a higher presence of lymphoid cells (170). Additionally, PD-L1 expression is variable, is associated with populations of infiltrating T cells, and may be more associated with sarcomatoid histology and a worse prognosis (171–174). Multiple clinical trials have sought to determine or are currently determining if MPM responds to immune mediated therapies (Table 2).

### CTLA4 inhibition

Tremelimumab is a selective human IgG2 monoclonal function blocking antibody against CTLA4 that blocks interaction with B7 and promotes anti-tumor effects of tumor infiltrating leukocytes (169). In the second-line setting, 2 out of 29 patients with MPM (7%) demonstrated a durable partial response to tremelimumab 15 mg/kg every 90 days (MESOT-TREM-2008) (175). Retrospective exposure-response analysis of data from melanoma suggested the dosing schedule of tremelimumab 15 mg/kg every 90 days resulted in underexposure to tremelimumab. A single-arm phase 2 study was then performed to evaluate the efficacy of tremelimumab 10 mg/kg every 4 weeks for 6 doses, followed by dosing every 12 weeks until disease progression. Four out of 29 patients were found to have a response and 15 out of 29 patients were found to have disease control with median duration of 10.9 months (95% CI: 8.2–13.6). Unfortunately, results of the double blind, placebo controlled DETERMINE (clinicaltrials.gov NCT01843374) study showed tremelimumab monotherapy is not superior to placebo for the primary endpoint of overall survival (tremelimumab *vs.* placebo median OS 7.7 *vs.* 7.3 mo; HR =0.92; 95% CI: 0.76–1.12, P=0.408) (176). Clinical studies that determine the efficacy of combining CTLA4 blockade with PD-1/PD-L1 blockade are ongoing (Table 2, clinicaltrials.gov NCT02899299 and NCT02588131).

### ***Programmed death-1/programmed death ligand-1 inhibition***

T lymphocytes express PD-1 which, upon binding to PD-L1 or PD-L2 on the surface of a potential target cell, inhibits cytotoxic killing of that target cell (169). MPM cells may inhibit the anti-tumor immune response and evade T lymphocyte mediated cell killing by expression of PD-L1 (169). Monoclonal antibodies against PD-1 (pembrolizumab and nivolumab) or PD-L1 (avelumab, atezolizumab, durvalumab) block the interaction of tumor cell expressed PD-L1 with PD-1 on the surface of T lymphocytes and thereby aim to inhibit the anti-tumor immune response. The Keynote-028 trial reported that 7 out of 25 PD-L1 positive MPM patients had a partial response to monotherapy with pembrolizumab (10 mg/kg every 2 weeks). The overall response rate of 28% and disease control rate of 76% are better than expected in the second line setting (177). In a single center phase II study, patients with MPM were treated in the second line setting with nivolumab 3 mg/kg every two weeks until progression or toxicity. Five out of 38 patients had a partial response and the disease control rate was 50% at 12 weeks (178). Lastly, a phase I study evaluating safety and treatment related toxicity of avelumab, a fully human anti-PD-L1 IgG antibody, reported an overall response rate of 14.3% in PD-L1 positive patients with unresectable MPM, and a response rate of 8% in patients with MPM without PD-L1 expression (179). These results indicate that targeting the PD-1/PD-L1 axis in MPM appears promising. Phase III trials evaluating PD-1/PD-L1 blockade in the setting of first-line therapy for MPM or relapsed disease and clinical studies combining CTLA4 inhibitors (above) with PD-1/PD-L1 blockade in patient with MPM are currently ongoing (Table 2). Further, efforts to identify predictors of response to immunotherapy, such as tumor molecular features or characterization of tumor immune infiltrates, could inform patient selection for immunotherapy.

### **Conclusions**

To date, the combination of pemetrexed, either cisplatin or carboplatin, and the optional addition of bevacizumab, is standard therapy for MPM in the frontline setting. Currently, there is no approved therapy for refractory disease, but gemcitabine and vinorelbine have activity in some patients, and immunotherapy is increasingly used off-label. Even with systemic therapy, median overall

survival is approximately one year and the chance of long-term survival is low. Many approaches are being pursued to evaluate novel therapeutic strategies to improve response rates, identify second-line therapies, determine if maintenance therapy is beneficial, and develop optimal regimens for the elderly and frail. The lack of “single driver mutations” identified in MPM presents a challenge to the development of molecular targeted therapies for MPM and highlights a need for a better understanding of MPM biology towards developing personalized approaches to therapy. Furthermore, the heterogeneity of MPM, the relatively low incidence of the disease, and the challenge to assess radiographic and clinical response to therapy pose barriers to developing more effective systemic therapies. Despite these challenges, mesothelin targeting, arginine depletion, and immunotherapy appear to be among the most promising of the emerging therapeutic strategies.

### **Acknowledgements**

None.

### **Footnote**

*Conflicts of Interest:* MR Mancuso has no conflicts of interest to declare. JW Neal has consulting or advisory roles with Clovis Oncology, Boehringer Ingelheim, ARMO Biosciences, Nektar Therapeutics, ARIAD pharmaceuticals/Takeda, Eli Lilly and Company, and Physician Resource Management. JW Neal receives research funding from Genentech/Roche, Merck, ArQule, Novartis, Boehringer Ingelheim, Nektar, and ARIAD. JW Neal does not have conflicts of interest to declare relating to employment, leadership, stocks and ownership interests, honoraria, patents, royalties, or other intellectual property, expert testimony, or receiving of travel expenses.

### **References**

1. Price B, Ware A. Time trend of mesothelioma incidence in the United States and projection of future cases: an update based on SEER data for 1973 through 2005. *Crit Rev Toxicol* 2009;39:576-88.
2. Taioli E, Wolf AS, Camacho-Rivera M, et al. Women with malignant pleural mesothelioma have a threefold better survival rate than men. *Ann Thorac Surg* 2014;98:1020-4.
3. Selikoff IJ, Hammond EC, Seidman H. Latency of asbestosis among insulation workers in the United

- States and Canada. *Cancer* 1980;46:2736-40.
4. Taioli E, Wolf AS, Flores RM. Meta-analysis of survival after pleurectomy decortication versus extrapleural pneumonectomy in mesothelioma. *Ann Thorac Surg* 2015;99:472-80.
  5. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Br J Ind Med* 1960;17:260-71.
  6. Nishikawa K, Takahashi K, Karjalainen A, et al. Recent mortality from pleural mesothelioma, historical patterns of asbestos use, and adoption of bans: a global assessment. *Environ Health Perspect* 2008;116:1675-80.
  7. Park EK, Takahashi K, Hoshuyama T, et al. Global magnitude of reported and unreported mesothelioma. *Environ Health Perspect* 2011;119:514-8.
  8. Carbone M, Baris YI, Bertino P, et al. Erionite exposure in North Dakota and Turkish villages with mesothelioma. *Proc Natl Acad Sci U S A* 2011;108:13618-23.
  9. Cavazza A, Travis LB, Travis WD, et al. Post-irradiation malignant mesothelioma. *Cancer* 1996;77:1379-85.
  10. De Bruin ML, Burgers JA, Baas P, et al. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. *Blood* 2009;113:3679-81.
  11. Deutsch M, Land SR, Begovic M, et al. An association between postoperative radiotherapy for primary breast cancer in 11 National Surgical Adjuvant Breast and Bowel Project (NSABP) studies and the subsequent appearance of pleural mesothelioma. *Am J Clin Oncol* 2007;30:294-6.
  12. Goodman JE, Nascarella MA, Valberg PA. Ionizing radiation: a risk factor for mesothelioma. *Cancer Causes Control* 2009;20:1237-54.
  13. Li X, Brownlee NA, Sporn TA, et al. Malignant (Diffuse) Mesothelioma in Patients With Hematologic Malignancies: A Clinicopathologic Study of 45 Cases. *Arch Pathol Lab Med* 2015;139:1129-36.
  14. Teta MJ, Lau E, Scurman BK, et al. Therapeutic radiation for lymphoma: risk of malignant mesothelioma. *Cancer* 2007;109:1432-8.
  15. Witherby SM, Butnor KJ, Grunberg SM. Malignant mesothelioma following thoracic radiotherapy for lung cancer. *Lung Cancer* 2007;57:410-3.
  16. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. *Nat Genet* 2011;43:1022-5.
  17. Nasu M, Emi M, Pastorino S, et al. High Incidence of Somatic BAP1 alterations in sporadic malignant mesothelioma. *J Thorac Oncol* 2015;10:565-76.
  18. Patel SC, Dowell JE. Modern management of malignant pleural mesothelioma. *Lung Cancer (Auckl)* 2016;7:63-72.
  19. Boutin C, Rey F, Gouvernet J, et al. Thoracoscopy in pleural malignant mesothelioma: a prospective study of 188 consecutive patients. Part 2: Prognosis and staging. *Cancer* 1993;72:394-404.
  20. Loddenkemper R. Thoracoscopy--state of the art. *Eur Respir J* 1998;11:213-21.
  21. Metintas M, Yildirim H, Kaya T, et al. CT Scan-Guided Abrams' Needle Pleural Biopsy versus Ultrasound-Assisted Cutting Needle Pleural Biopsy for Diagnosis in Patients with Pleural Effusion: A Randomized, Controlled Trial. *Respiration* 2016;91:156-63.
  22. Adams RF, Gray W, Davies RJ, et al. Percutaneous image-guided cutting needle biopsy of the pleura in the diagnosis of malignant mesothelioma. *Chest* 2001;120:1798-802.
  23. Beauchamp HD, Kundra NK, Aranson R, et al. The role of closed pleural needle biopsy in the diagnosis of malignant mesothelioma of the pleura. *Chest* 1992;102:1110-2.
  24. Boutin C, Schlessler M, Frenay C, et al. Malignant pleural mesothelioma. *Eur Respir J* 1998;12:972-81.
  25. Chakrabarti B, Ryland I, Sheard J, et al. The role of Abrams percutaneous pleural biopsy in the investigation of exudative pleural effusions. *Chest* 2006;129:1549-55.
  26. Maskell NA, Gleeson FV, Davies RJ. Standard pleural biopsy versus CT-guided cutting-needle biopsy for diagnosis of malignant disease in pleural effusions: a randomised controlled trial. *Lancet* 2003;361:1326-30.
  27. Hjerpe A, Ascoli V, Bedrossian C, et al. Guidelines for 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. *Cytojournal* 2015;12:26.
  28. Flores RM, Krug LM, Rosenzweig KE, et al. Induction chemotherapy, extrapleural pneumonectomy, and postoperative high-dose radiotherapy for locally advanced malignant pleural mesothelioma: a phase II trial. *J Thorac Oncol* 2006;1:289-95.
  29. Van Schil PE, Baas P, Gaafar R, et al. Trimodality therapy for malignant pleural mesothelioma: results from an EORTC phase II multicentre trial. *Eur Respir J* 2010;36:1362-9.
  30. Gupta V, Mychalczak B, Krug L, et al. Hemithoracic radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2005;63:1045-52.
  31. Baldini EH, Richards WG, Gill RR, et al. Updated

- patterns of failure after multimodality therapy for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg* 2015;149:1374-81.
32. Sugarbaker DJ, Richards WG, Bueno R. Extrapleural pneumonectomy in the treatment of epithelioid malignant pleural mesothelioma: novel prognostic implications of combined N1 and N2 nodal involvement based on experience in 529 patients. *Ann Surg* 2014;260:577-80; discussion 580-2.
  33. Linton A, Pavlakis N, O'Connell R, et al. Factors associated with survival in a large series of patients with malignant pleural mesothelioma in New South Wales. *Br J Cancer* 2014;111:1860-9.
  34. Meyerhoff RR, Yang CF, Speicher PJ, et al. Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database. *J Surg Res* 2015;196:23-32.
  35. Musk AW, Olsen N, Alfonso H, et al. Predicting survival in malignant mesothelioma. *Eur Respir J* 2011;38:1420-4.
  36. Tsao AS, Wistuba I, Roth JA, et al. Malignant pleural mesothelioma. *J Clin Oncol* 2009;27:2081-90.
  37. 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.
  38. 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.
  39. Cantwell BM, Franks CR, Harris AL. A phase II study of the platinum analogues JM8 and JM9 in malignant pleural mesothelioma. *Cancer Chemother Pharmacol* 1986;18:286-8.
  40. Chahinian AP, Antman K, Goutsou M, et al. Randomized phase II trial of cisplatin with mitomycin or doxorubicin for malignant mesothelioma by the Cancer and Leukemia Group B. *J Clin Oncol* 1993;11:1559-65.
  41. Ellis P, Davies AM, Evans WK, et al. The use of chemotherapy in patients with advanced malignant pleural mesothelioma: a systematic review and practice guideline. *J Thorac Oncol* 2006;1:591-601.
  42. Samson MK, Wasser LP, Borden EC, et al. Randomized comparison of cyclophosphamide, imidazole carboxamide, and adriamycin versus cyclophosphamide and adriamycin in patients with advanced stage malignant mesothelioma: a Sarcoma Intergroup Study. *J Clin Oncol* 1987;5:86-91.
  43. Sørensen PG, Bach F, Bork E, et al. Randomized trial of doxorubicin versus cyclophosphamide in diffuse malignant pleural mesothelioma. *Cancer Treat Rep* 1985;69:1431-2.
  44. Berghmans T, Paesmans M, Lalami Y, et al. Activity of chemotherapy and immunotherapy on malignant mesothelioma: a systematic review of the literature with meta-analysis. *Lung Cancer* 2002;38:111-21.
  45. van Meerbeeck JP, Gaafar R, Manegold C, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005;23:6881-9.
  46. Hughes A, Calvert P, Azzabi A, et al. Phase I clinical and pharmacokinetic study of pemetrexed and carboplatin in patients with malignant pleural mesothelioma. *J Clin Oncol* 2002;20:3533-44.
  47. Castagneto B, Botta M, Aitini E, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). *Ann Oncol* 2008;19:370-3.
  48. Ceresoli GL, Castagneto B, Zucali PA, et al. Pemetrexed plus carboplatin in elderly patients with malignant pleural mesothelioma: combined analysis of two phase II trials. *Br J Cancer* 2008;99:51-6.
  49. Katirtzoglou N, Gkiozos I, Makrilia N, et al. Carboplatin plus pemetrexed as first-line treatment of patients with malignant pleural mesothelioma: a phase II study. *Clin Lung Cancer* 2010;11:30-5.
  50. Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemo-naïve patients with malignant pleural mesothelioma: results of the International Expanded Access Program. *J Thorac Oncol* 2008;3:756-63.
  51. Lee CW, Murray N, Anderson H, et al. Outcomes with first-line platinum-based combination chemotherapy for malignant pleural mesothelioma: a review of practice in British Columbia. *Lung Cancer* 2009;64:308-13.
  52. Byrne MJ, Davidson JA, Musk AW, et al. Cisplatin and gemcitabine treatment for malignant mesothelioma: a phase II study. *J Clin Oncol* 1999;17:25-30.
  53. Nowak AK, Byrne MJ, Williamson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer* 2002;87:491-6.
  54. Kalmadi SR, Rankin C, Kraut MJ, et al. Gemcitabine and cisplatin in unresectable malignant mesothelioma of the pleura: a phase II study of the Southwest Oncology Group (SWOG 9810). *Lung Cancer* 2008;60:259-63.

55. Ak G, Metintas S, Akarsu M, et al. The effectiveness and safety of platinum-based pemetrexed and platinum-based gemcitabine treatment in patients with malignant pleural mesothelioma. *BMC Cancer* 2015;15:510.
56. Favaretto AG, Aversa SM, Paccagnella A, et al. Gemcitabine combined with carboplatin in patients with malignant pleural mesothelioma: a multicentric phase II study. *Cancer* 2003;97:2791-7.
57. Castagneto B, Zai S, Dongiovanni D, et al. Cisplatin and gemcitabine in malignant pleural mesothelioma: a phase II study. *Am J Clin Oncol* 2005;28:223-6.
58. van Haarst JM, Baas P, Manegold C, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. *Br J Cancer* 2002;86:342-5.
59. Steele JP, Shamash J, Evans MT, et al. Phase II study of vinorelbine in patients with malignant pleural mesothelioma. *J Clin Oncol* 2000;18:3912-7.
60. Fennell DA, JP CS, Shamash J, et al. Phase II trial of vinorelbine and oxaliplatin as first-line therapy in malignant pleural mesothelioma. *Lung Cancer* 2005;47:277-81.
61. Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer* 2009;63:94-7.
62. Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. *Lancet* 2008;371:1685-94.
63. Ray M, Kindler HL. Malignant Pleural Mesothelioma: An Update on Biomarkers and Treatment. *Chest* 2009;136:888-96.
64. Vogelzang NJ. Chemotherapy for malignant pleural mesothelioma. *Lancet* 2008;371:1640-2.
65. Manegold C, Symanowski J, Gatzemeier U, et al. Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. *Ann Oncol* 2005;16:923-7.
66. Jassem J, Ramlau R, Santoro A, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. *J Clin Oncol* 2008;26:1698-704.
67. Ceresoli GL, Zucali PA, Gianoncelli L, et al. Second-line treatment for malignant pleural mesothelioma. *Cancer Treat Rev* 2010;36:24-32.
68. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009;374:1432-40.
69. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol* 2012;13:247-55.
70. Jing XQ, Zhou L, Sun XD, et al. Pemetrexed Maintenance Therapy Following Bevacizumab-Containing First-Line Chemotherapy in Advanced Malignant Pleural Mesothelioma: A Case Report and Literatures Review. *Medicine (Baltimore)* 2016;95:e3351.
71. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med* 1971;285:1182-6.
72. D'Amato RJ, Loughnan MS, Flynn E, et al. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci U S A* 1994;91:4082-5.
73. Remon J, Reguart N, Corral J, et al. Malignant pleural mesothelioma: new hope in the horizon with novel therapeutic strategies. *Cancer Treat Rev* 2015;41:27-34.
74. Buikhuisen WA, Scharpfenecker M, Griffioen AW, et al. A Randomized Phase II Study Adding Axitinib to Pemetrexed-Cisplatin in Patients with Malignant Pleural Mesothelioma: A Single-Center Trial Combining Clinical and Translational Outcomes. *J Thorac Oncol* 2016;11:758-68.
75. Grosso F, Steele N, Novello S, et al. Nintedanib plus pemetrexed/cisplatin in patients with MPM: Phase II findings from the placebo-controlled LUME-Meso trial. Vienna: 17th IASLC World Conference on Lung Cancer 2016 Contract No.: ID #4191
76. Heckman CA, Holopainen T, Wirzenius M, et al. The tyrosine kinase inhibitor cediranib blocks ligand-induced vascular endothelial growth factor receptor-3 activity and lymphangiogenesis. *Cancer Res* 2008;68:4754-62.
77. Wedge SR, Kendrew J, Hennequin LF, et al. AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. *Cancer Res* 2005;65:4389-400.
78. Campbell NP, Kunnavakkam R, Leigh N, et al. Cediranib in patients with malignant mesothelioma: a phase II trial of the University of Chicago Phase II Consortium. *Lung Cancer* 2012;78:76-80.
79. Garland LL, Chansky K, Wozniak AJ, et al. Phase II study of cediranib in patients with malignant pleural mesothelioma: SWOG S0509. *J Thorac Oncol*

- 2011;6:1938-45.
80. Tsao AS, Moon J, Moon II, et al. A phase I study of cediranib (NSC #732208) in combination with cisplatin and pemetrexed in chemo-naïve patients with malignant pleural mesothelioma (SWOG S0905). *J Clin Oncol* 2013;31 suppl:abstr 7527.
  81. Laurie SA, Gupta A, Chu Q, et al. Brief report: a phase II study of sunitinib in malignant pleural mesothelioma. the NCIC Clinical Trials Group. *J Thorac Oncol* 2011;6:1950-4.
  82. Jahan T, Gu L, Kratzke R, et al. Vatalanib in malignant mesothelioma: a phase II trial by the Cancer and Leukemia Group B (CALGB 30107). *Lung Cancer* 2012;76:393-6.
  83. Dubey S, Jänne PA, Krug L, et al. A phase II study of sorafenib in malignant mesothelioma: results of Cancer and Leukemia Group B 30307. *J Thorac Oncol* 2010;5:1655-61.
  84. Papa S, Popat S, Shah R, et al. Phase 2 study of sorafenib in malignant mesothelioma previously treated with platinum-containing chemotherapy. *J Thorac Oncol* 2013;8:783-7.
  85. Pignochino Y, Dell'Aglio C, Inghilleri S, et al. The combination of sorafenib and everolimus shows antitumor activity in preclinical models of malignant pleural mesothelioma. *BMC Cancer* 2015;15:374.
  86. Kothmaier H, Quehenberger F, Halbwedl I, et al. EGFR and PDGFR differentially promote growth in malignant epithelioid mesothelioma of short and long term survivors. *Thorax* 2008;63:345-51.
  87. Langerak AW, De Laat PA, Van Der Linden-Van Beurden CA, et al. Expression of platelet-derived growth factor (PDGF) and PDGF receptors in human malignant mesothelioma in vitro and in vivo. *J Pathol* 1996;178:151-60.
  88. Li Q, Wang W, Yamada T, et al. Pleural mesothelioma instigates tumor-associated fibroblasts to promote progression via a malignant cytokine network. *Am J Pathol* 2011;179:1483-93.
  89. Dagher R, Cohen M, Williams G, et al. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. *Clin Cancer Res* 2002;8:3034-8.
  90. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001;344:1031-7.
  91. Vogelzang NJ, Porta C, Mutti L. New agents in the management of advanced mesothelioma. *Semin Oncol* 2005;32:336-50.
  92. Porta C, Mutti L, Tassi G. Negative results of an Italian Group for Mesothelioma (G.I.Me.) pilot study of single-agent imatinib mesylate in malignant pleural mesothelioma. *Cancer Chemother Pharmacol* 2007;59:149-50.
  93. Villano JL, Husain AN, Stadler WM, et al. A Phase II trial of imatinib mesylate in patients (pts) with malignant mesothelioma (MM). *J Clin Oncol* 2004;22:Abstract 7200.
  94. Mathy A, Baas P, Dalesio O, et al. Limited efficacy of imatinib mesylate in malignant mesothelioma: a phase II trial. *Lung Cancer* 2005;50:83-6.
  95. Pietras K, Rubin K, Sjoblom T, et al. Inhibition of PDGF receptor signaling in tumor stroma enhances antitumor effect of chemotherapy. *Cancer Res* 2002;62:5476-84.
  96. Bertino P, Porta C, Barbone D, et al. Preliminary data suggestive of a novel translational approach to mesothelioma treatment: imatinib mesylate with gemcitabine or pemetrexed. *Thorax* 2007;62:690-5.
  97. Tsao AS, Harun N, Lee JJ, et al. Phase I trial of cisplatin, pemetrexed, and imatinib mesylate in chemo-naïve patients with unresectable malignant pleural mesothelioma. *Clin Lung Cancer* 2014;15:197-201.
  98. Ali Y, Lin Y, Gharibo MM, et al. Phase I and pharmacokinetic study of imatinib mesylate (Gleevec) and gemcitabine in patients with refractory solid tumors. *Clin Cancer Res* 2007;13:5876-82.
  99. Jagadeeswaran R, Ma PC, Seiwert TY, et al. Functional analysis of c-Met/hepatocyte growth factor pathway in malignant pleural mesothelioma. *Cancer Res* 2006;66:352-61.
  100. Dazzi H, Hasleton PS, Thatcher N, et al. Malignant pleural mesothelioma and epidermal growth factor receptor (EGF-R). Relationship of EGF-R with histology and survival using fixed paraffin embedded tissue and the F4, monoclonal antibody. *Br J Cancer* 1990;61:924-6.
  101. Destro A, Ceresoli GL, Falleni M, et al. EGFR overexpression in malignant pleural mesothelioma. An immunohistochemical and molecular study with clinicopathological correlations. *Lung Cancer* 2006;51:207-15.
  102. Edwards JG, Swinson DE, Jones JL, et al. EGFR expression: associations with outcome and clinicopathological variables in malignant pleural mesothelioma. *Lung Cancer* 2006;54:399-407.
  103. Garland LL, Rankin C, Gandara DR, et al. Phase II study of erlotinib in patients with malignant pleural mesothelioma: a Southwest Oncology Group Study. *J Clin Oncol* 2007;25:2406-13.
  104. Govindan R, Kratzke RA, Herndon JE, 2nd, et al. Gefitinib in patients with malignant mesothelioma: a phase II study by the Cancer and Leukemia Group B. *Clin*

- Cancer Res 2005;11:2300-4.
105. O'Byrne KJ, Edwards JG, Waller DA. Clinico-pathological and biological prognostic factors in pleural malignant mesothelioma. *Lung Cancer* 2004;45 Suppl 1:S45-8.
  106. Okuda K, Sasaki H, Kawano O, et al. Epidermal growth factor receptor gene mutation, amplification and protein expression in malignant pleural mesothelioma. *J Cancer Res Clin Oncol* 2008;134:1105-11.
  107. Jänne PA, Taffaro ML, Salgia R, et al. Inhibition of epidermal growth factor receptor signaling in malignant pleural mesothelioma. *Cancer Res* 2002;62:5242-7.
  108. Rodgers SJ, Ferguson DT, Mitchell CA, et al. Regulation of PI3K effector signalling in cancer by the phosphoinositide phosphatases. *Biosci Rep* 2017;37.
  109. Lo Iacono M, Monica V, Righi L, et al. Targeted next-generation sequencing of cancer genes in advanced stage malignant pleural mesothelioma: a retrospective study. *J Thorac Oncol* 2015;10:492-9.
  110. Afriansyah A, Hamid AR, Mochtar CA, et al. Targeted Therapy for Metastatic Renal Cell Carcinoma. *Acta Med Indones* 2016;48:335-47.
  111. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012;366:520-9.
  112. Jancic J, Duric V, Ivancevic N, et al. Current Use of mTOR Inhibitors for the Treatment of Subependymal Giant Cell Astrocytomas and Epilepsy in Patients with TSC. *Curr Med Chem* 2016;23:4260-9.
  113. Ohmoto A, Rokutan H, Yachida S. Pancreatic Neuroendocrine Neoplasms: Basic Biology, Current Treatment Strategies and Prospects for the Future. *Int J Mol Sci* 2017;18.
  114. Ou SH, Moon J, Garland LL, et al. SWOG S0722: phase II study of mTOR inhibitor everolimus (RAD001) in advanced malignant pleural mesothelioma (MPM). *J Thorac Oncol* 2015;10:387-91.
  115. Dolly SO, Wagner AJ, Bendell JC, et al. Phase I Study of Apatolisib (GDC-0980), Dual Phosphatidylinositol-3-Kinase and Mammalian Target of Rapamycin Kinase Inhibitor, in Patients with Advanced Solid Tumors. *Clin Cancer Res* 2016;22:2874-84.
  116. Kanteti R, Riehm JJ, Dhanasingh I, et al. PI3 Kinase Pathway and MET Inhibition is Efficacious in Malignant Pleural Mesothelioma. *Sci Rep* 2016;6:32992.
  117. Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet* 2016;48:407-16.
  118. Zauderer MG, Bott M, McMillan R, et al. Clinical characteristics of patients with malignant pleural mesothelioma harboring somatic BAP1 mutations. *J Thorac Oncol* 2013;8:1430-3.
  119. Jensen DE, Proctor M, Marquis ST, et al. BAP1: a novel ubiquitin hydrolase which binds to the BRCA1 RING finger and enhances BRCA1-mediated cell growth suppression. *Oncogene* 1998;16:1097-112.
  120. Sowa ME, Bennett EJ, Gygi SP, et al. Defining the human deubiquitinating enzyme interaction landscape. *Cell* 2009;138:389-403.
  121. Kelly WK, O'Connor OA, Krug LM, et al. Phase I study of an oral histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in patients with advanced cancer. *J Clin Oncol* 2005;23:3923-31.
  122. Krug LM, Kindler HL, Calvert H, et al. Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): a phase 3, double-blind, randomised, placebo-controlled trial. *Lancet Oncol* 2015;16:447-56.
  123. Ramalingam SS, Belani CP, Ruel C, et al. Phase II study of belinostat (PXD101), a histone deacetylase inhibitor, for second line therapy of advanced malignant pleural mesothelioma. *J Thorac Oncol* 2009;4:97-101.
  124. LaFave LM, Beguelin W, Koche R, et al. Loss of BAP1 function leads to EZH2-dependent transformation. *Nat Med* 2015;21:1344-9.
  125. Petrilli AM, Fernandez-Valle C. Role of Merlin/NF2 inactivation in tumor biology. *Oncogene* 2016;35:537-48.
  126. Pachter JA, Kolev VN, Schunselaar L, et al. Abstract 4236: FAK inhibitor VS-6063 (defactinib) targets mesothelioma cancer stem cells, which are enriched by standard of care chemotherapy. *Cancer Res* 2015;75:Abstract 4236.
  127. Shimizu T, Fukuoka K, Takeda M, et al. A first-in-Asian phase 1 study to evaluate safety, pharmacokinetics and clinical activity of VS-6063, a focal adhesion kinase (FAK) inhibitor in Japanese patients with advanced solid tumors. *Cancer Chemother Pharmacol* 2016;77:997-1003.
  128. Soria JC, Gan HK, Blagden SP, et al. A phase I, pharmacokinetic and pharmacodynamic study of GSK2256098, a focal adhesion kinase inhibitor, in patients with advanced solid tumors. *Ann Oncol* 2016;27:2268-74.
  129. Wu J, Liu T, Rios Z, et al. Heat Shock Proteins and Cancer. *Trends Pharmacol Sci* 2017;38:226-56.
  130. Wang Y, Trepel JB, Neckers LM, et al. STA-9090, a small-molecule Hsp90 inhibitor for the potential treatment of cancer. *Curr Opin Investig Drugs* 2010;11:1466-76.
  131. Curran MP, McKeage K. Bortezomib: a review of its use

- in patients with multiple myeloma. *Drugs* 2009;69:859-88.
132. Wang Y, Rishi AK, Puliappadamba VT, et al. Targeted proteasome inhibition by Velcade induces apoptosis in human mesothelioma and breast cancer cell lines. *Cancer Chemother Pharmacol* 2010;66:455-66.
  133. Fennell DA, McDowell C, Busacca S, et al. Phase II clinical trial of first or second-line treatment with bortezomib in patients with malignant pleural mesothelioma. *J Thorac Oncol* 2012;7:1466-70.
  134. O'Brien ME, Gaafar RM, Popat S, et al. Phase II study of first-line bortezomib and cisplatin in malignant pleural mesothelioma and prospective validation of progression free survival rate as a primary end-point for mesothelioma clinical trials (European Organisation for Research and Treatment of Cancer 08052). *Eur J Cancer* 2013;49:2815-22.
  135. Chang K, Pastan I. Molecular cloning of mesothelin, a differentiation antigen present on mesothelium, mesotheliomas, and ovarian cancers. *Proc Natl Acad Sci U S A* 1996;93:136-40.
  136. Bera TK, Pastan I. Mesothelin is not required for normal mouse development or reproduction. *Mol Cell Biol* 2000;20:2902-6.
  137. Chowdhury PS, Viner JL, Beers R, et al. Isolation of a high-affinity stable single-chain Fv specific for mesothelin from DNA-immunized mice by phage display and construction of a recombinant immunotoxin with anti-tumor activity. *Proc Natl Acad Sci U S A* 1998;95:669-74.
  138. Fujisaka Y, Kurata T, Tanaka K, et al. Phase I study of amatuximab, a novel monoclonal antibody to mesothelin, in Japanese patients with advanced solid tumors. *Invest New Drugs* 2015;33:380-8.
  139. Hassan R, Cohen SJ, Phillips M, et al. Phase I clinical trial of the chimeric anti-mesothelin monoclonal antibody MORAb-009 in patients with mesothelin-expressing cancers. *Clin Cancer Res* 2010;16:6132-8.
  140. Hassan R, Kindler HL, Jahan T, et al. Phase II clinical trial of amatuximab, a chimeric antimesothelin antibody with pemetrexed and cisplatin in advanced unresectable pleural mesothelioma. *Clin Cancer Res* 2014;20:5927-36.
  141. Zhao XY, Subramanyam B, Sarapa N, et al. Novel Antibody Therapeutics Targeting Mesothelin In Solid Tumors. *Clin Cancer Drugs* 2016;3:76-86.
  142. Perez HL, Cardarelli PM, Deshpande S, et al. Antibody-drug conjugates: current status and future directions. *Drug Discov Today* 2014;19:869-81.
  143. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012;367:1783-91.
  144. Five-Year Survival Data Demonstrating Durable Responses From a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma. *Clin Adv Hematol Oncol* 2016;14:6.
  145. Updated Efficacy and Safety Data From the AETHERA Trial of Consolidation With Brentuximab Vedotin After Autologous Stem Cell Transplant (ASCT) in Hodgkin Lymphoma Patients at High Risk of Relapse. *Clin Adv Hematol Oncol* 2016;14:17-8.
  146. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015;385:1853-62.
  147. Ritchie M, Tchistiakova L, Scott N. Implications of receptor-mediated endocytosis and intracellular trafficking dynamics in the development of antibody drug conjugates. *mAbs* 2013;5:13-21.
  148. Golfier S, Kopitz C, Kahnert A, et al. Anetumab ravtansine: a novel mesothelin-targeting antibody-drug conjugate cures tumors with heterogeneous target expression favored by bystander effect. *Mol Cancer Ther* 2014;13:1537-48.
  149. Kupchan SM, Komoda Y, Court WA, et al. Maytansine, a novel antileukemic ansa macrolide from *Maytenus ovatus*. *J Am Chem Soc* 1972;94:1354-6.
  150. Kovtun YV, Audette CA, Ye Y, et al. Antibody-drug conjugates designed to eradicate tumors with homogeneous and heterogeneous expression of the target antigen. *Cancer Res* 2006;66:3214-21.
  151. Blumenschein GR, Hassan R, Moore KN, et al. Phase I study of anti-mesothelin antibody drug conjugate anetumab ravtansine (AR). *J Clin Oncol* 2016;34:abstr 2509.
  152. Scales SJ, Gupta N, Pacheco G, et al. An antimesothelin-monomethyl auristatin e conjugate with potent antitumor activity in ovarian, pancreatic, and mesothelioma models. *Mol Cancer Ther* 2014;13:2630-40.
  153. Zhang Y, Xiang L, Hassan R, et al. Synergistic antitumor activity of taxol and immunotoxin SSIP in tumor-bearing mice. *Clin Cancer Res* 2006;12:4695-701.
  154. Griffon-Etienne G, Boucher Y, Brekken C, et al. Taxane-induced apoptosis decompresses blood vessels and lowers interstitial fluid pressure in solid tumors: clinical implications. *Cancer Res* 1999;59:3776-82.
  155. Holden SA, Lan Y, Pardo AM, et al. Augmentation of antitumor activity of an antibody-interleukin 2

- immunocytokine with chemotherapeutic agents. *Clin Cancer Res* 2001;7:2862-9.
156. Hollevoet K, Mason-Osann E, Liu XF, et al. In vitro and in vivo activity of the low-immunogenic antimesothelin immunotoxin RG7787 in pancreatic cancer. *Mol Cancer Ther* 2014;13:2040-9.
  157. Hassan R, Bullock S, Premkumar A, et al. Phase I study of SS1P, a recombinant anti-mesothelin immunotoxin given as a bolus I.V. infusion to patients with mesothelin-expressing mesothelioma, ovarian, and pancreatic cancers. *Clin Cancer Res* 2007;13:5144-9.
  158. Kreitman RJ, Hassan R, Fitzgerald DJ, et al. Phase I trial of continuous infusion anti-mesothelin recombinant immunotoxin SS1P. *Clin Cancer Res* 2009;15:5274-9.
  159. Hassan R, Miller AC, Sharon E, et al. Major cancer regressions in mesothelioma after treatment with an anti-mesothelin immunotoxin and immune suppression. *Sci Transl Med* 2013;5:208ra147.
  160. Zhang J, Khanna S, Jiang Q, et al. Efficacy of Anti-mesothelin Immunotoxin RG7787 plus Nab-Paclitaxel against Mesothelioma Patient-Derived Xenografts and Mesothelin as a Biomarker of Tumor Response. *Clin Cancer Res* 2017;23:1564-74.
  161. Szlosarek PW, Klabatsa A, Pallaska A, et al. In vivo loss of expression of argininosuccinate synthetase in malignant pleural mesothelioma is a biomarker for susceptibility to arginine depletion. *Clin Cancer Res* 2006;12:7126-31.
  162. Szlosarek PW, Steele JP, Nolan L, et al. Arginine Deprivation With Pegylated Arginine Deiminase in Patients With Argininosuccinate Synthetase 1-Deficient Malignant Pleural Mesothelioma: A Randomized Clinical Trial. *JAMA Oncol* 2017;3:58-66.
  163. Beddowes E, Spicer J, Chan PY, et al. Phase 1 Dose-Escalation Study of Pegylated Arginine Deiminase, Cisplatin, and Pemetrexed in Patients With Argininosuccinate Synthetase 1-Deficient Thoracic Cancers. *J Clin Oncol* 2017;35:1778-85.
  164. Ascierto PA, Scala S, Castello G, et al. Pegylated arginine deiminase treatment of patients with metastatic melanoma: results from phase I and II studies. *J Clin Oncol* 2005;23:7660-8.
  165. Glazer ES, Piccirillo M, Albino V, et al. Phase II study of pegylated arginine deiminase for nonresectable and metastatic hepatocellular carcinoma. *J Clin Oncol* 2010;28:2220-6.
  166. Izzo F, Marra P, Beneduce G, et al. Pegylated arginine deiminase treatment of patients with unresectable hepatocellular carcinoma: results from phase I/II studies. *J Clin Oncol* 2004;22:1815-22.
  167. Yang TS, Lu SN, Chao Y, et al. A randomised phase II study of pegylated arginine deiminase (ADI-PEG 20) in Asian advanced hepatocellular carcinoma patients. *Br J Cancer* 2010;103:954-60.
  168. Bersanelli M, Buti S. From targeting the tumor to targeting the immune system: Transversal challenges in oncology with the inhibition of the PD-1/PD-L1 axis. *World J Clin Oncol* 2017;8:37-53.
  169. Buchbinder EI, Desai A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. *Am J Clin Oncol* 2016;39:98-106.
  170. Linton A, van Zandwijk N, Reid G, et al. Inflammation in malignant mesothelioma - friend or foe? *Ann Cardiothorac Surg* 2012;1:516-22.
  171. 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.
  172. Cedrés S, Ponce-Aix S, Zugazagoitia J, et al. Analysis of Expression of Programmed Cell Death 1 Ligand 1 (PD-L1) in Malignant Pleural Mesothelioma (MPM). *PloS One* 2015;10:e0121071.
  173. 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.
  174. 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.
  175. Calabrò 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.
  176. Kindler H, L., Scherpereel A, Calabrò L, et al. Tremelimumab as second- or third-line treatment of unresectable malignant mesothelioma (MM): Results from the global, double-blind, placebo-controlled DETERMINE study. *J Clin Oncol* 2016;34:abstr 8502.
  177. Alley EW, Molife LR, Santoro A, et al. Abstract CT103: Clinical safety and efficacy of pembrolizumab (MK-3475) in patients with malignant pleural mesothelioma: Preliminary results from KEYNOTE-028. *Cancer Res* 2015;75:CT103-CT.
  178. Quispel-Janssen J, Zago G, Schouten R, et al. OA13.01

- A Phase II Study of Nivolumab in Malignant Pleural Mesothelioma (NivoMes): with Translational Research (TR) Biopsies. *J Thorac Oncol* 2017;12:S292-S3.
179. Hassan R, Thomas A, Patel MR, et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with advanced unresectable mesothelioma from the JAVELIN solid

tumor phase Ib trial: Safety, clinical activity, and PD-L1 expression. *J Clin Oncol* 2016;34:abstr 8503.

**Cite this article as:** Mancuso MR, Neal JW. Novel systemic therapy against malignant pleural mesothelioma. *Transl Lung Cancer Res* 2017;6(3):295-314. doi: 10.21037/tlcr.2017.06.01