Targeting angiogenesis for patients with unresectable malignant pleural mesothelioma

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ABSTRACT

Malignant pleural mesothelioma (MPM) is a global health issue, the principal cause of which is exposure to asbestos. The prevalence is anticipated to rise over the next 2 decades, particularly in developing countries, due to the 30–50-year latency period between exposure to asbestos and carcinogenic development. Unresectable MPM has a poor prognosis and limited treatment options and, as such, there is a broad range of therapeutic targets of interest, including angiogenesis, immune checkpoints, mesothelin, as well as chemotherapeutic agents. Recently, the results of several randomized trials in the first-line setting combining antiangiogenic agents with chemotherapy have been reported. This review examines the scientific rationale for targeting angiogenesis in the treatment of unresectable MPM and analyzes recent clinical results with antiangiogenic agents in development (bevacizumab, nintedanib, and cediranib) for the management of MPM.

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Introduction

Mesothelioma is an uncommon, aggressive cancer, originating from cells lining the mesothelial surfaces. The majority of cases (>90%) originate in the pleura; however, less commonly, it can originate in the peritoneum, pericardium, or tunica vaginalis of the testis [1]. It is estimated that there are ~43,000 deaths worldwide from malignant pleural mesothelioma (MPM) each year [2], although this number may be much higher due to the incidence of unreported cases in developing countries [3]. The principal cause of MPM is exposure to asbestos [4]. Although asbestos use is partially or completely banned in more than 60 countries worldwide, it continues to be produced and used in some countries, notably Russia, China, and Brazil [5]. There is a long latency period of around 30–50 years between asbestos exposure and disease presentation [6]. As such, it is anticipated that MPM will remain a global health issue and it is even predicted that the global incidence of MPM may increase in the next 2 decades [7,8].

Symptoms of MPM include dyspnea, chest pain, weight loss, and fatigue [1]. These symptoms often appear late in the disease course and, given their nonspecific nature, can contribute to many cases being diagnosed at an advanced stage. Diagnosis of MPM can be challenging, as it is uncommon and can be difficult to distinguish from other benign and malignant conditions. Furthermore, patients with MPM have a poor prognosis; the median duration of survival from diagnosis of unresectable disease is around 8–14 months [9].

MPM is classified by histologic subtype: the 3 main subtypes are epithelioid (accounting for the majority of MPM in around 60% of cases), sarcomatoid (around 20% of cases), and biphasic, which has elements of both epithelioid and sarcomatoid (around 20% of cases) [4]. The underlying histologic subtype correlates with
survival times, with the longest survival among those with epithelioid and poorest among those with sarcomatoid histology [4]. Immunohistochemical markers, including calretinin, cytokeratins 5/6, WT1, and podoplanin (D2-40) are histologic diagnostic markers that are commonly used to distinguish mesothelioma from other differentials [6]; however, there is currently a lack of validated biomarkers available to guide treatment selection and prognosis.

While surgery may be an option for some patients with early stage disease, the majority of patients do not undergo surgery due to advanced stage and/or comorbidities, and, depending on their country of origin, the role of cytoreductive surgery remains controversial. For unresectable or advanced stage MPM patients, chemotherapy with cisplatin/pemetrexed is the only Food and Drug Administration (FDA)- or European Medicines Agency (EMA)-approved treatment option, having shown an overall survival (OS) improvement versus cisplatin alone (12.1 vs 9.3 months) in a phase III trial in 456 patients [6,10]. Carboplatin/pemetrexed is an accepted alternative to cisplatin for patients unable to receive cisplatin [11]. However, MPM tumors are relatively chemotherapy-resistant and there is no US FDA- or EMA-approved second-line therapy; at present, it is advised that patients with relapsed/refractory disease should be offered enrollment into an appropriate clinical trial [6]. The role of second-line chemotherapy has been evaluated in a prospective, randomized phase III trial (n = 243) comparing pemetrexed with best supportive care in patients previously treated with a first-line regimen (not including pemetrexed). The study showed a statistically significant increase in objective response rate, disease control rate, and time to progression for pemetrexed, but a lack of benefit in OS [12]. In standard practice, other chemotherapy agents including gemcitabine and vinorelbine have been used in the salvage setting.

In light of the poor prognosis and limited regulatory-approved treatment options, unresectable MPM is an area of high unmet need. As a result, there are a number of potential therapies in development [13]. In the salvage setting, anecdotally, patients with MPM may be receiving checkpoint inhibitors, despite the lack of regulatory approval [14-16]. There is a broad range of therapeutic targets of interest, including angiogenesis, immune checkpoints, mesothelin, as well as chemotherapeutic agents.

In patients with previously treated MPM, there have been several studies evaluating immune checkpoint inhibition, using antibodies that block cytotoxic T-lymphocyte-associated antigen (CTLA)-4, programmed cell death protein (PD)-1, or its ligand, PD-L1. Tremelimumab, an anti-CTLA-4 monoclonal antibody, demonstrated modest clinical activity in 2 single-arm phase II studies in patients with malignant mesothelioma that had progressed after a first-line platinum-based regimen [17,18]. Unfortunately, in the phase IIb randomized DETERMINED trial in 569 patients with previously treated malignant mesothelioma, there was no significant difference in OS between tremelimumab and placebo [19].

The anti-PD-1 antibodies pembrolizumab and nivolumab have shown clinical activity in patients with previously treated MPM. In KEYNOTE-028, pembrolizumab was tested in the PD-L1 positive population, which comprised 46% of evaluable patients and was defined as expression in ≥1% of tumor cells [15]. Pembrolizumab was associated with an overall response rate of 28%, with median response duration of 9.2 months and median OS of 18.0 months in patients with PD-L1-positive MPM. Grade 3/4 treatment-related adverse events (AEs) were reported in 20% of patients [14]. In an interim analysis of a phase II trial in patients with MPM or peritoneal mesothelioma (irrespective of PD-L1 expression) that had progressed on/after pemetrexed/platinum, pembrolizumab was associated with a response rate of 21% and the response did not correlate with PD-L1 expression. Grade 3/4 toxicity included pneumonitis, fatigue, and adrenal insufficiency (6% each) and there were 2 deaths: one due to autoimmune hepatitis and one of unknown cause [20].

For dual checkpoint inhibition, the MAPS2 trial evaluated nivolumab alone or in combination with the anti-CTLA-4 antibody, ipilimumab, in MPM patients who had relapsed after 1 or 2 prior lines of therapy. The overall response rate was 18.5% with nivolumab and 27.8% with the combination; median OS was 13.6 months with nivolumab and had not yet been reached with the combination. However, more grade 3/4 AEs occurred in the combination arm than with nivolumab alone (26.2% vs 12.7%); in addition, there were 3 treatment-related deaths in the combination arm [16]. Based on these results, pembrolizumab (Category 2A), and nivolumab (with or without ipilimumab; category 2A for both) are recommended in the USA NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Malignant Pleural Mesothelioma V2.2019 as options for second-line and beyond (subsequent) systemic therapy in patients with MPM [21]. A Category 2A recommendation means that NCCN has uniform consensus (≥85%) that the intervention is appropriate, based upon lower-level evidence (eg, phase 2 trials). On August 21, 2018, Japan was the first country to give regulatory approval to nivolumab in chemotherapy-refractory MPM patients based on the salvage trial called MERIT [22].

While the immune checkpoint inhibitors are currently under investigation in the front-line setting for unresectable MPM, antiangiogenic agents have demonstrated benefit in combination with chemotherapy in some MPM patients. In this review, we examine the current state-of-the-art of antiangiogenic therapies in the treatment of unresectable MPM by reviewing the principal agents in development, their supporting data, and their role in the management of MPM.

Rationale for targeting angiogenesis

Angiogenesis is a complex, multifaceted process, which is regulated by a variety of signaling proteins, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF) [4,23]. As angiogenesis is essential for tumor growth, targeting of angiogenesis has long been recognized as a therapeutic option for multiple cancer types. Inhibition of the receptors that VEGF and bFGF bind (VEGFR and FGFR [fibroblast growth factor receptor]) has been reported to reduce the formation of new blood vessels within tumors, while inhibition of FGFR and the receptor that PDGF binds (PDGFR), impairs blood vessel maturation and maintenance [24-26].

There is additional evidence that targeting angiogenesis may be of particular relevance in MPM. High microvessel density (a means of assessing angiogenesis) is associated with poor prognosis in MPM [27] and patients with MPM have also been shown to have higher VEGF serum levels compared with those who had been exposed to asbestos but not developed MPM [28]. Pathways other than VEGF are also thought to be involved in MPM. For example, in addition to increased VEGF, mesothelioma cell lines produce high levels of FGF [29]. Furthermore, the presence of proangiogenic factors, including VEGF, FGF-1, and FGF-2, was increased in mesothelioma tumor samples compared with nonneoplastic mesothelium. High FGF-2 expression showed particular correlation with tumor aggressiveness and poor prognosis [30]. Signaling via Src and Abl kinases have also been shown to be involved in MPM cell migration [31,32]. VEGF-independent angiogenic factors, progranulin- and granulin-like protein, have also been identified in mesothelioma cell lines [33]. Angiopoietin and Tie families have primary roles in vascular development and are deregulated in many cancers [34,35]. Angiopoietin-1 (Ang-1) stimulates mesothelioma cell growth and migration and serum levels are increased significantly in patients with MPM compared with
an asbestos-exposed population without malignancies [38], CD26, a type II transmembrane glycoprotein with known dipeptidyl peptidase 4 (DPP-4) activity, is also involved in tumorigenesis in various tumors [37,38]. CD26/DPP-4 is preferentially overexpressed in MPM cells but not in normal mesothelial cells [39] and its level of expression correlates with improved clinical outcomes and therapeutic response to chemotherapy for MPM [40]. Involvement of CD26/DPP-4 in angiogenesis has been demonstrated in preclinical and clinical studies [41].

**First-line treatment of MPM with antiangiogenics**

In the first-line setting, antiangiogenic agents have been combined with the current standard of care, cisplatin/pemetrexed. Three main agents—bevacizumab, nintedanib, and cediranib—each with different modes of action and at different stages of development have been reported.

**Bevacizumab**

Bevacizumab is a monoclonal antibody that binds to VEGF, thereby disrupting a key signaling pathway that drives angiogenesis. First approved in the USA in 2004, it is currently indicated for the treatment of a number of cancers including colorectal cancer, non–small cell lung cancer (NSCLC) (excluding squamous), renal cell carcinoma, cervical cancer, and ovarian, fallopian, or peritoneal cancer. Additionally, bevacizumab is approved for glioblastoma in the USA and breast cancer in Europe [42,43].

Initial assessment of bevacizumab in combination with chemotherapy for MPM in phase II trials was not associated with clear improvements in efficacy. One phase II study in 108 evaluable patients with malignant mesothelioma showed that adding bevacizumab to cisplatin/gemcitabine did not lead to any difference in progression-free survival (PFS) or OS compared with chemotherapy alone [44]. It was suggested that the choice of chemotherapy may have contributed to the observed lack of efficacy: preclinical data indicated a potential negative interaction between gemcitabine and bevacizumab. In a subsequent phase II single-arm trial, previously untreated, unresectable MPM patients (n = 76) treated with bevacizumab and carboplatin/pemetrexed exhibited median PFS and OS of 6.9 and 15.3 months, respectively [45]. As such, the study failed to achieve its primary endpoint of 9-month median PFS, a 50% improvement in comparison to historical data for standard chemotherapy. A separate phase II trial in 53 previously untreated patients with advanced MPM showed that the combination of cisplatin/pemetrexed and bevacizumab was associated with a 6-month PFS rate of 56% and a median OS of 14.8 months. The study failed to achieve its primary endpoint of a 33% improvement in 6-month PFS rate versus historical controls of chemotherapy alone [46].

However, the larger, phase II/III, open-label Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) trial demonstrated that adding bevacizumab to cisplatin/pemetrexed conferred significant clinical benefits versus chemotherapy alone [47]. A total of 448 patients with unresectable MPM who had not been previously treated with chemotherapy were randomized to cisplatin/pemetrexed with or without bevacizumab for up to six cycles. Subsequent maintenance bevacizumab was permitted until disease progression or intolerable AEs. Addition of bevacizumab to chemotherapy significantly improved the primary endpoint of OS versus chemotherapy alone (median 18.8 v 16.1 months; hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.62–0.95; P = 0.0167). This increase occurred despite a significantly lower rate of poststudy treatment in the chemotherapy plus bevacizumab group (62% received further chemotherapy and 5% received further bevacizumab v 72% in the chemotherapy alone group receiving further chemotherapy). There were no significant interactions when OS was analyzed by prognostic factors, such as age, performance status, or histologic subtype. The HR for OS was 0.64 (95% CI 0.40–1.02) in patients with sarcomatoid/mixed histology and 0.82 (0.64–1.06) in patients with epithelioid histology. PFS was also significantly improved in those receiving bevacizumab (median 9.2 v 7.3 months; HR 0.61 [0.50–0.75]; P < 0.0001) [47]. The addition of bevacizumab to first-line chemotherapy treatment did impact tolerability; the rate of grade ≥3 AEs was higher in the bevacizumab arm than the chemotherapy only arm (71.2% v 62.1%). This increase was attributable to higher rates of AEs known to be associated with bevacizumab, including hypertension (all-grade: 56.3% v 1.3%), hemorrhage (41.0% v 7.1%), elevated creatinine (38.7% v 28.1%), and thromboembolic events (7.2% v 1.3%). Moreover, treatment discontinuations due to AEs were significantly higher in the bevacizumab arm than the chemotherapy alone arm (24.3% v 6.0%; P < 0.0001); however, the authors noted that the AE profile with bevacizumab appeared generally manageable and did not appear to affect the quality of life [47]. Based on these data, the triplet regimen is now accepted as an alternative to platinum-pemetrexed for patients with unresectable MPM who have not been previously treated with chemotherapy.

**Nintedanib**

Nintedanib is a multtargeted angiokinase inhibitor with activity against VEGFR 1, 2, and 3, PDGFR α/β, and FGF receptors. Nintedanib also inhibits Flt-3, Lck, Src, and Abl kinase signaling [48,49]. It is approved in the USA and Europe for the treatment of idiopathic pulmonary fibrosis; in Europe, it is also approved (in combination with docetaxel) for advanced adenocarcinoma NSCLC after first-line chemotherapy [50-52].

Compared with bevacizumab, which only inhibits VEGF, it was hypothesized that targeting other antiangiogenic pathways shown to be involved in MPM (e.g., FGFR, PDGFR, Src, Abl) with nintedanib could enhance efficacy. Preclinically, nintedanib has provided sustained inhibition of VEGFR-2 activation [48]. Nintedanib has also been shown to inhibit MPM tumor growth in human xenograft models and reduce colony-forming capacity and migratory activity in MPM cell lines [53,54].

Nintedanib has been assessed for the treatment of MPM in the phase II/III LUME-Meso trial [49,55]. The phase II portion enrolled patients with unresectable nonsarcomatoid MPM (stratified by histologic subtype: epithelioid or biphasic) who had not been previously treated with chemotherapy. Patients were randomized to nintedanib or placebo in combination with cisplatin/pemetrexed for up to six cycles, followed by continued nintedanib or placebo monotherapy. A total of 87 patients were randomized to treatment (44 to nintedanib [39 epithelioid histology; 5 biphasic] and 43 to placebo [38 epithelioid; 5 biphasic]) [55]. Addition of nintedanib to cisplatin/pemetrexed improved PFS (median 9.4 v 5.7 months; HR 0.54; 95% CI 0.33–0.87; P = 0.010) and was associated with a trend toward improved OS (median 18.3 v 14.2 months; HR 0.77; 95% CI 0.46–1.29; P = 0.319) compared with placebo. This effect was consistent across subgroups, with the exception of patients with biphasic histology. Among patients with epithelioid histology, median PFS with nintedanib versus placebo was 9.7 versus 5.7 months (HR 0.49; 95% CI 0.30–0.82; P = 0.006) and median OS was 20.6 versus 15.2 months (HR 0.70; 95% CI 0.40–1.21; P = 0.197) [55]. A treatment effect could not be estimated for the patients with biphasic histology because of the small number of patients in this subgroup. Addition of nintedanib to cisplatin/pemetrexed was also associated with a trend toward improvement in forced vital capacity (a measure of pulmonary function) [56].

The most common AEs (of any grade) were nausea (84.1% with nintedanib v 87.8% with placebo), fatigue (75.0% v 90.2%), and di-
arrhea (70.5% vs 36.6%) [55]. While the incidence of diarrhea was higher than reported in a lung cancer trial where nintedanib was given with docetaxel [57], rates were similar to those reported for nintedanib in combination with a doublet chemotherapy [58,59]. Moreover, the majority of cases were of low grade and were generally reversible and manageable with dose interruption. Indeed, no patients discontinued treatment due to diarrhea. Neutropenia was the most common grade ≥3 AE (43.2% with nintedanib vs 12.2% with placebo); however, the incidence of febrile neutropenia was low (4.5% vs 0%) [55]. Liver enzyme elevations were also reported more frequently in the nintedanib arm than the placebo arm (increased alanine transaminase levels, all-grade [grade ≥3]: 38.6% vs 13.6%; v 2.4%; [2.4%]; increased aspartate transaminase levels: 29.5% [0%] v 2.4% [0%]). These elevations were generally reversible and manageable with dose interruption. Notably, the AEs associated with antiangiogenic agents were generally balanced between treatment arms or occurred less frequently in the nintedanib arm (nintedanib vs placebo, bleeding: 11.4% v 12.2%; GI perforation: 0 v 2.4%; thromboembolism: 9.1% v 17.1%, and venous thromboembolism: 6.8% v 14.6%). AEs leading to discontinuation occurred in 6.8% in the nintedanib arm and 17.1% in the placebo arm [55]. Exploratory biomarker analysis among the epithelioid population did not show any associations with treatment benefit.

However, the encouraging findings of the phase II LUME-Meso trial were not confirmed in the phase III part of the trial. In the phase III trial, 458 patients with histologically confirmed, unresected epithelioid MPM not previously treated with chemotherapy, and a life expectancy of ≥3 months were randomized to nintedanib 200 mg twice daily plus cisplatin/pemetrexed (n = 229) or placebo plus cisplatin/pemetrexed (n = 229) for a maximum of six cycles, followed by nintedanib or placebo maintenance for patients without progressive disease (NCT01907100) [49,60]. The primary endpoint was PFS and the key secondary endpoint was OS (Fig. 1). At baseline, the median age in both treatment groups was 66 years; >60% patients had stage III or IV tumors at screening. The results of the phase III part of the LUME-Meso trial did not support the earlier findings of the phase II study, as the primary endpoint was not met. Investigator-assessed median PFS for nintedanib versus placebo was 6.8 versus 7.0 months (HR [95% CI] 1.01 [0.79–1.30]; P = 0.914). Median OS (interim analysis) for nintedanib versus placebo was 14.4 versus 16.1 months (HR [95% CI] 1.12 [0.79–1.58]; P = 0.538). The safety profile of nintedanib was manageable and consistent with its profile in other studies, and its addition to the chemotherapy regimen did not compromise quality of life. This study has been discontinued as per the study protocol [60].

Cediranib

Cediranib is an inhibitor of VEGFR, PDGFR, and stem cell factor receptor (c-Kit). It has not yet been approved for medicinal use, but is in development for MPM and in other settings such as ovarian cancer. The phase I SWOG S0905 trial assessed cediranib in combination with cisplatin/pemetrexed in patients with MPM not previously treated with chemotherapy (any histologic subtype) [61]. A total of 20 patients were enrolled. Cediranib plus cisplatin/pemetrexed was considered reasonably well tolerated, with the main grade 3/4 AEs being gastrointestinal toxicity, dehydration, and hematological disorders. The combination showed promising preliminary efficacy (median PFS was 8.6 months [modified RECIST] and median OS was 16.2 months). A phase II S0905 trial further evaluated cediranib plus cisplatin/pemetrexed (compared with cisplatin/pemetrexed alone) [62]. This trial enrolled 92 patients (25% biphasic/sarcomatoid) and demonstrated that cediranib combined with cisplatin/pemetrexed improved modified RECIST response rates (53% v 20%, P = 0.01) and had a trend toward improving RECIST ITT PFS (median PFS 7.2 v 5.6, HR 0.69, P = 0.096). The S0905 phase II was designed to detect a difference in PFS at the 1-sided 0.1 level [62].

Other agents

Imatinib (a PDGFR inhibitor) combined with cisplatin/pemetrexed in patients with MPM who had not been previously treated with chemotherapy showed some clinical benefit (supporting PDGFR as a relevant target); however, tolerability was poor [63]. Axitinib (an inhibitor of VEGFR-1, -2, -3, PDGFR, and c-Kit) showed a lack of clinical benefit in a phase II study in which patients with MPM who had not been previously treated with chemotherapy were randomized to cisplatin/pemetrexed plus axitinib or observation [64,65].
Table 1
Study of antiangiogenic agents as monotherapy in patients with MPM

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study design, patients, and treatment</th>
<th>Efficacy</th>
<th>Safety/tolerability</th>
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<tr>
<td>Sunitinib [72]</td>
<td>• Single-arm phase II&lt;br&gt;• Eligible patients (N=51); MPM; progression after first-line CT; ECOG PS 0–1; measurable disease&lt;br&gt;• Treatment: sunitinib 50 mg daily for the first 4 weeks of a 6-week cycle until progression, unacceptable toxicity, or patient withdrawal</td>
<td>• PR in 12%&lt;br&gt;• Median OS: 6.1 months</td>
<td>• Most frequent toxicities were grade 1–3 fatigue (89%), nausea (68%), anorexia (62%), and vomiting (39%)</td>
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<td>Sunitinib [73]</td>
<td>• Single-arm phase II&lt;br&gt;• Eligible patients (N=35 [17 in cohort 1; 18 in cohort 2]): MPM, ECOG PS 0–2; measurable disease; cohort 1: ≤3 prior lines of CT; cohort 2: CT-naïve&lt;br&gt;• Treatment: sunitinib 50 mg daily for the first 4 weeks of a 6-week cycle until progression, unacceptable toxicity, or patient withdrawal</td>
<td>• Cohort 1: one PR; median PFS 2.8 months, median OS 8.3 months&lt;br&gt;• Cohort 2: no responses; median PFS 2.7 months, median OS 0.7 months</td>
<td>• Most frequent toxicities were fatigue, GI complaints, and HFS&lt;br&gt;• Hematological toxicity was mild (one grade 4 event)</td>
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<tr>
<td>Cediranib [74]</td>
<td>• Single-arm phase II&lt;br&gt;• Eligible patients (N=54): MPM; previous platinum CT; ECOG PS 0–2&lt;br&gt;• Treatment: cediranib 45 mg/d until progression or unacceptable toxicity</td>
<td>• 47 evaluable patients&lt;br&gt;• PR in 9%&lt;br&gt;• Median OS 9.5 months&lt;br&gt;• Median PFS 2.6 months</td>
<td>• Most common toxicities were fatigue (64%), diarrhea (64%), and hypertension (70%)</td>
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<td>Cediranib [75]</td>
<td>• Single-arm phase II&lt;br&gt;• Eligible patients (N=51): unresectable MM; ≤1 prior CT; ECOG PS 0–1; measurable disease&lt;br&gt;• Treatment: cediranib 45 mg/d (reduced to 30 mg/d in protocol amendment) in a 28 day cycle (minimum two cycles)</td>
<td>• 50 evaluable patients&lt;br&gt;• PR in 10%&lt;br&gt;• Median PFS 1.8 months&lt;br&gt;• Median OS 4.4 months</td>
<td>• Most common grade 3/4 toxicities were fatigue (2/3%), hypertension (22%), and diarrhea (8%)</td>
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<td>Sorafenib [76]</td>
<td>• Single-arm phase II&lt;br&gt;• Eligible patients (N=51): unresectable MM; ≤1 prior CT; ECOG PS 0–1&lt;br&gt;• Treatment: sorafenib 400 mg twice daily until PD or unacceptable toxicity</td>
<td>• 50 evaluable patients&lt;br&gt;• PR in 6%&lt;br&gt;• Median PFS 3.6 months&lt;br&gt;• Median OS 9.7 months</td>
<td>• Most common grade 3/4 toxicities were fatigue (2/6%), rash (12%), and dyspnea (6%)</td>
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<tr>
<td>Sorafenib [77]</td>
<td>• Single-arm phase II&lt;br&gt;• Eligible patients (N=56): unresectable MPM; prior first-line platinum-pemetrexed CT; ECOG PS 0–2; measurable disease&lt;br&gt;• Treatment: sorafenib 400 mg twice daily until PD, unacceptable toxicity, or withdrawal of consent</td>
<td>• 53 evaluable patients&lt;br&gt;• PR in 6%&lt;br&gt;• Median PFS 5.1 months&lt;br&gt;• Median OS 9.0 months</td>
<td>• Most common grade 3/4 toxicities were fatigue (15%), PPE (13%), and rash (9%)</td>
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<td>Dovitinib [78]</td>
<td>• Single-arm phase II&lt;br&gt;• Eligible patients (N=12): advanced MPM; prior platinum-antifolate CT and ≤1 additional line of systemic therapy; ECOG PS 0–2; measurable disease&lt;br&gt;• Treatment: dovitinib 500 mg/day (5 days on, 2 days off [28-day cycles]) until PD, unacceptable toxicity or patient request</td>
<td>• One unconfirmed PR&lt;br&gt;• Median PFS 2.6 months (3-month PR rate: 50%)&lt;br&gt;• Median OS 4 months&lt;br&gt;• Trial halted early</td>
<td>• Most common grade ≥3 toxicities were fatigue (50%), dyspnea (42%), pain (17%), venous thromboembolism (17%), and rash (17%)</td>
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<td>Thalidomide [79]</td>
<td>• Single-arm phase II&lt;br&gt;• Eligible patients (N=40): MPM, performance status (WHO criteria) 0–2, prior CT allowed&lt;br&gt;• Treatment: increasing doses of thalidomide (100–400 mg) until progression or toxicity</td>
<td>• 6-month PF rate: 27.5%&lt;br&gt;• Median survival: 230 days</td>
<td>• Main toxicity was constipation (18/40) and 2 patients developed grade 2 neurotoxicity</td>
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CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; HFS, hand-foot syndrome; MM, malignant mesothelioma; MPM, malignant pleural mesothelioma; OS, overall survival; PD, progressive disease; PF, progression free; PFS, progression-free survival; PR, partial response; PPE, palmar-plantar erythrodysesthesia; WHO, World Health Organization.

Treatment of relapsed/recurrent MPM with antiangiogenics

Some of the earlier trials exploring antiangiogenic therapies assessed these agents as monotherapy, predominantly in the relapsed/recurrent setting (after at least one line of treatment). However, trial results were generally disappointing, with either a lack of clinical benefit (modest effects, at best) or poor tolerability, precluding further development. Key results from these trials are summarized in Table 1.

Conclusions and future directions

Antiangiogenic therapy has yielded the first positive data in front-line MPM for a decade and represents a new prospect for improving patients’ prognosis. Nevertheless, this approach has yielded mixed results. While the use of bevacizumab in the MAPS trial was positive and promising for antiangiogenesis, encouraging phase II nintedanib data could not be confirmed in the subsequent phase III study of nintedanib, which showed disappointing results. More data are required to establish how to maximize the potential benefits of bevacizumab therapy in this setting and to determine the appropriate patient selection criteria. For example, validated predictive/prognostic biomarkers would be beneficial. However, such biomarkers remain to be identified for the main antiangiogenic agents and results from analyses of ongoing trials are awaited.

Currently, antiangiogenic therapy has been combined with conventional chemotherapy in the first-line setting. One key question to address will be if there are differences between chemotherapy regimens and their suitability for coadministration with antiangiogenic treatment. For example, in the NSCLC setting, the addition of bevacizumab to paclitaxel/carboplatin significantly improved OS.
<table>
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<tr>
<th>Study (phase)</th>
<th>Mechanism of action</th>
<th>Treatment</th>
<th>Patients</th>
<th>N</th>
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<td><strong>First-line setting</strong></td>
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| LUME-Meso: nintedanib in mesothelioma (III) | Antiangiogenesis (VEGFR, PDGFR, and FGFR TKI) | Nintedanib + pemetrexed/cisplatin v placebo + pemetrexed/cisplatin | • MPM (epithelioid)  
• No prior systemic CT | 458 (actual) | NCT01907100; completed |
| Checkmate-743: nivolumab + ipilimumab in MPM (III) | Immunotherapy (anti-PD-1 + anti-CTLA-4) | Nivolumab + ipilimumab v pemetrexed/cisplatin (or carboplatin)  
• Unresectable MPM  
• No prior CT | 600 (estimated) | NCT02899299; active, not recruiting |
| Pembrolizumab in advanced MPM (II) | Immunotherapy (anti-PD-1) | Cisplatin/pemetrexed v Cisplatin/pemetrexed + pembrolizumab v pembrolizumab | • Advanced MPM  
• No prior CT | 126 (estimated) | NCT02784171; recruiting |
| Durvalumab in unresectable MPM (II) | Immunotherapy (anti-PD-L1) | Durvalumab + pemetrexed/cisplatin (up to six cycles) then durvalumab alone (stable or responding disease) | • Unresectable MPM  
• No prior systemic therapy | 55 (estimated) | NCT02891995; active, not recruiting |
| ARTEMIS: ataxinib in combination with CT (II) | Antimesothelin | Ataxinib + pemetrexed/cisplatin (then ataxinib maintenance) v placebo + pemetrexed/cisplatin (then placebo maintenance) | • Unresectable MPM (epithelioid)  
• No prior systemic therapy | 108 (actual) | NCT02357147; active, not recruiting |
| ATOMIC-Meso: ADI-PEG 20 in MPM (II/III) | Arginine depletion | ADI-PEG 20 + pemetrexed/cisplatin v placebo + pemetrexed/cisplatin | • MPM  
• No prior systemic therapy  
• Tumor sample for ASS1 status determination | 386 (estimated) | NCT02709512; recruiting |
| **First- or later-line setting** | | | | | |
| Brentuximab vedotin in CD30+ MM (II) | Anti-CD30 | Brentuximab vedotin (single-arm) | • Unresectable MM (any primary site)  
• CD30+ expression  
• CT-naïve or -refractory | 50 (estimated) | NCT0007030; recruiting |
| Low dose gemcitabine + cisplatin (II) | Chemotherapy | 6-hour infusion of gemcitabine (250 mg/m²) + cisplatin | • Unresectable MPM | 26 (estimated) | NCT01869023; active, not recruiting |
| **Second- or later-line setting** | | | | | |
| Nintedanib in recurrent MPM (II) | Antiangiogenesis (VEGFR, PDGFR, and FGFR TKI) | Nintedanib (single-arm) | • MPM  
• Prior platinum-based CT (no more than 2 prior systemic therapies) | 55 (estimated) | NCT02568449; recruiting |
| PROMISE-Meso: pembrolizumab in advanced pretreated MPM (III) | Immunotherapy (anti-PD-1) | Pembrolizumab v gemcitabine or vinorelbine | • MPM (all subtypes)  
• Progression after or on previous platinum-based CT | 144 (estimated) | NCT02991482; active, not recruiting |
| MAPS2: nivolumab alone or in combination with ipilimumab for MPM (II) | Immunotherapy (anti-PD-1) | Nivolumab v nivolumab + ipilimumab | • Unresectable MPM  
• Received 1 or 2 systemic CT lines | 125 (actual) | NCT02716272; active, not recruiting |
| Pembrolizumab in patients with MM (II) | Immunotherapy (anti-PD-1) | Pembrolizumab (single-arm) | • MM (pleural or peritoneal); epithelial, sarcomatoid, or biphasic  
• PD on/after pemetrexed/cisplatin or carboplatin | 65 (actual) | NCT02393971; active, not recruiting |
| Durvalumab + tremelimumab in MPM (II) | Immunotherapy (anti-CTLA-4 + anti-PD-L1) | Tremelimumab + durvalumab (single-arm) | • Unresectable MPM  
• PD after ≥ 1 line of CT that included a first-line platinum agent | 40 (estimated) | NCT03075552; recruiting |
| INITIATE: nivolumab + ipilimumab in MPM (II) | Immunotherapy (anti-PD-1 + anti-CTLA-4) | Nivolumab + ipilimumab (single-arm) | • MPM (any subtype)  
• PD after ≥ 1 prior systemic treatment with a platinum-based doublet | 33 (estimated) | NCT03048474; active, not recruiting |
| CRS-207 + pembrolizumab in MPM (II) | Immunotherapy (anti-PD-1) | CRS-207 + pembrolizumab (single-arm) | • MPM (epithelioid/biphasic)  
• Progressed after 1–2 prior anticancer therapies | 35 (estimated) | NCT03175712; active, not recruiting |

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<tr>
<th>Study (phase)</th>
<th>Mechanism of action</th>
<th>Treatment</th>
<th>Patients</th>
<th>N</th>
<th>NCT; status</th>
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| IMC-A12 monotherapy in MM (II) | Anti-IGF-1R | IMC-A12 monotherapy (single-arm) | • Pleural or peritoneal MM  
• Previously treated on ≥1 platinum-containing CT regimen or refused CT | 20 (actual) | NCT0160458; completed |
| Gemcitabine + imatinib in MM (II) | FDGFR TKI | Gemcitabine + imatinib mesylate (single-arm) | • Pleural or peritoneal MM expressing PDGFR-beta and/or c-Kit  
• Progression after a pemetrexed-based CT | 22 (actual) | NCT02303899; active, not recruiting |
| Atezolizumab + vinorelbine as second-line treatment for MPM (II) | Antimesothelin | Atezolizumab + vinorelbine vinorelbine | • Advanced or metastatic MPM overexpressing mesothelin  
• Progressed on first-line treatment of platinum + pemetrexed | 248 (actual) | NCT02610140; active, not recruiting |
| VBM: vinorelbine in mesothelioma (II) | CT | Vinorelbine v placebo (active symptom control) | • MPM  
• Prior treatment with first-line standard platinum doublet-based CT only | 200 (estimated) | NCT02139090; recruiting |
| Lurbinectedin monotherapy in MPM (II) | CT | Lurbinectedin (single-arm) | • MPM  
• PD on or after one line of platinum-based CT | 43 (estimated) | NCT03213301; recruiting |
| ATREUS: trabectedin in MPM (II) | CT | Trabectedin (single-arm) | • Unresectable MPM  
• Not more than one previous CT | 141 (estimated) | NCT02194231; recruiting |
| Transarterial chemoperfusion of cisplatin, methotrexate, gemcitabine (II) | CT | Chemoperfusion with cisplatin + methotrexate + gemcitabine | • MPM  
• Failed to respond to first-line CT or refuses first-line CT | 36 (estimated) | NCT02611037; recruiting |
| Alisertib in salvage MM (II) | Aurora A kinase inhibitor | Alisertib (single-arm) | • MM  
• Received ≥1 prior pemetrexed-based CT (up to 4 prior lines of systemic therapy are allowed) | 28 (actual) | NCT02293003; active, not recruiting |

**Maintenance**

| NEMO: nintedanib as switch maintenance (II) | Antiangiogenesis (VEGFR, PDGFR, and FGF TKI) | Nintedanib v placebo | • Unresectable MPM  
• Response or stable disease after first-line platinum-pemetrexed CT | 116 (estimated) | NCT02863055; recruiting |
| Maintenance NGR-htTNF (II) | Vascular targeting | NGR-htTNF + BSC v placebo + BSC | • MPM (epithelial, sarcomatoid, mixed, unknown)  
• Non-PD after first-line pemetrexed-based CT | 100 (estimated) | NCT01358084; active, not recruiting |
| Maintenance pemetrexed (II) | CT | Pemetrexed v observation | • MPM (epithelial, sarcomatoid, mixed)  
• No progression after 4 courses of first-line CT | 68 (actual) | NCT01085630; active, not recruiting |

ASS1, argininosuccinate synthase 1; BSC, best supportive care; CT, chemotherapy; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; FGF, fibroblast growth factor receptor; MM, malignant mesothelioma; MPM, malignant pleural mesothelioma; PDGFR, platelet-derived growth factor receptor; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.
versus chemotherapy alone in 2 clinical trials [66,67]. However, the addition of bevacizumab to gemcitabine/cisplatin was not associated with an OS benefit [68].

Another question is whether antiangiogenic therapy could be combined effectively with other agents. Angiogenic factors have roles in both blood vessel formation and regulation of the immune system. For example, there are preclinical data to suggest that VEGF may suppress the immune response: high levels of VEGF can inhibit dendritic cell functions and VEGF has been shown to directly modulate T-cell proliferation, migration, and activation [69]. Moreover, it has been hypothesized that combining antiangiogenic agents with immunotherapy may produce synergistic effects. In murine tumor models, nintedanib in combination with an anti-PD-1 showed additive activity in an anti-PD-1 sensitive model and was associated with synergistic activity in an anti-PD-1 refractory model [70]. Furthermore, in a recent randomized phase III trial in patients with first-line advanced NSCLC, the addition of bevacizumab and the PD-L1 inhibitor atezolizumab to chemotherapy was more effective than the addition of either agent alone [71]. This hypothesis is now being examined in clinical trials in mesothelioma patients: an ongoing phase I trial is assessing the combination of nintedanib and the PD-L1 inhibitor, pembrolizumab, in patients with multiple tumor types, including MPM (NCT02856425). In addition, a phase II study is underway evaluating atezolizumab and bevacizumab in pleural and peritoneal mesothelioma patients (NCT03074513).

Finally, the role of antiangiogenics in the maintenance setting is also of interest. Several of the ongoing trials in the first-line setting are designed so that patients without progressive disease will continue maintenance therapy after completion of chemotherapy (Table 2). For example, in LUME-Meso, patients without progressive disease in the nintedanib plus cisplatin/pemetrexed arm will continue nintedanib monotherapy after completion of up to six cycles of cisplatin/pemetrexed. Other trials are looking at the feasibility of antiangiogenesis as switch maintenance: in the NEMO trial (EORTC 08112), patients with response or stable disease after first-line platinum-pemetrexed chemotherapy will be randomized to receive nintedanib or placebo as maintenance therapy (NCT02863055).

In conclusion, antiangiogenic therapy has the potential to improve the outlook for patients with MPM, but further data and identification of the patients that can benefit are needed to establish how to optimize the use of this treatment approach.

Conflicts of interest

AT has served on advisory boards for Bristol-Myers Squibb, Genentech, Roche, Ariad, Boehringer Ingelheim, AstraZeneca, and Huron; and has received research support from AstraZeneca, Bristol-Myers Squibb, Lilly, Millenium/Takeda, Seattle Genetics, Ariad, Boehringer Ingelheim, Polaris, Epizyme, and Merck.

TN has received honoraria from Boehringer Ingelheim, MSD, Olympus, Kyorin, and Ono.

AKN has received personal fees for consulting on clinical trials for Bayer and Douglas, for being on a clinical trial steering committee for Roche and for serving on advisory boards for Bristol-Myers Squibb; has received research funding from Douglas and AstraZeneca; and has received travel funding from Boehringer Ingelheim.

SP has received an institutional grant from the National Health Service for the research infrastructure during the conduct of the study; has received institutional research funding from Boehringer Ingelheim, Epizyme, Bristol-Myers Squibb, Clovis Oncology, Roche, Lilly, Takeda, and Pfizer; has received honoraria from Boehringer Ingelheim, Roche, Takeda, AstraZeneca, and Chugai Pharma; has received personal fees for consulting roles for Boehringer Ingelheim, Bristol Myers Squibb, Roche, Takeda, AstraZeneca, Novartis, Pfizer, MSD, Guardant Health, and AbbVie; and has received personal fees and nonfinancial support for travel, accommodation and expenses from Boehringer Ingelheim, Bristol-Myers Squibb, and MSD.

GVS has received personal fees from AstraZeneca, Eli Lilly, MSD, and Roche.

JHV has served on advisory boards for AstraZeneca, Boehringer Ingelheim, Exelixis, Genentech, GlaxoSmithKline, Guardant Health, Hengrui, Lilly, Novartis, Spectrum, EMD Serono, and Synta; has received research support from AstraZeneca, Bayer, GlaxoSmithKline, and Spectrum; and has received royalties and licensing fees from Spectrum.

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[71] Socinski MA, Jotte RM, Capuzzo F, et al. Overall survival (OS) analysis of IMpower150, a randomized Phase 3 study of atezolizumab (atezolizumab) + chemotherapy (chemo) + bevacizumab (bev) vs chemo + bev in 1L nonsquamous (NSQ) NSCLC. J Clin Oncol 2018;36(suppl):abstract 9002.