# Targeted therapies in malignant pleural mesothelioma: a review of clinical studies

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**Malignant pleural mesothelioma (MPM) is an aggressive tumor with poor prognosis, whose exposure to asbestos fibers is the main etiology. The incidence of MPM is anticipated to increase worldwide during the first half of this century. MPM is notoriously refractory to most treatments, and the only standard of care is cisplatin and antifolate first-line chemotherapy. The urgent need for additional therapeutic agents, in parallel with advances in the knowledge of the molecular events of oncogenesis, has resulted in the development of the so-called 'targeted agents' that specifically inhibit critical pathways in malignant cells and in their microenvironment. We carried out a comprehensive review of the literature from January 2000 to May 2010 on studies that assessed targeted agents for the systemic treatment of MPM. Although tyrosine kinase inhibitors directed against the epidermal growth factor and the platelet-derived growth factor receptors did not show significant clinical activity in phase II studies, some other targeted therapies seemed promising, notably histone deacetylase inhibitors and antiangiogenic agents. However, none of these has yet reached daily practice. That is the reason why efforts must continue in the area of clinical and translational research for MPM. *Anti-Cancer Drugs* 22:199–205 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumor, whose main etiology is the exposure to asbestos fibers. Although asbestos exposure can be environmental [1–3], most cases result from occupational exposures. The occurrence of MPM parallels the exploitation and use of asbestos, with a mean latency period of approximately 40 years [4–6]. Thus, the incidence of MPM is increasing in most developed countries, and is expected to rise during the next 10 years in Europe [7,8]. Although the incidence of MPM should then decrease in developed countries, it is expected to increase in developing countries, where the use of asbestos is regulated poorly, if at all [9]. Consequently, MPM will remain for many years a major health problem on a worldwide scale.

Generally, MPM has a poor prognosis, with a median overall survival (OS) without treatment of less than 12 months [4,10] and is notoriously refractory to treatments. Neither surgery nor radiotherapy alone has resulted in increased survival. Multimodal strategies involving surgery, radiotherapy, and systemic treatments were explored in early-stage MPM patients only in retrospective and phase II clinical studies. In multicenter phase II trials [11–13], median OS ranged from 16.8 to 19.8 months, which is not very impressive, although patients were exposed to significant toxicities. The Mesothelioma and Radical Surgery trial was the first and only randomized study to compare trimodality therapy to chemotherapy alone, but this was a pilot study to assess the feasibility of such a randomized trial in MPM [14].

During the last decade, two phase III randomized trials were conducted in the setting of first-line chemotherapy for unresectable MPM. First, Vogelzang *et al.* [15] randomized *222* patients with MPM to cisplatin alone and *226* patients to a combination of cisplatin and pemetrexed, a multitargeted antifolate. Combination therapy was associated with a significantly better median OS (12.1 vs. 9.3 months; $P = 0.02$) compared with cisplatin alone [15]. In 2005, the results of a second phase III trial were published [16]. This trial compared a chemotherapy doublet with cisplatin and raltitrexed, another folate pathway inhibitor, with cisplatin monotherapy. The combination arm showed an overall median survival of 11.4 versus 8.8 months ($P = 0.048$) [16]. Taken together, these results led to the adoption of the combination of cisplatin and an antifolate (pemetrexed or raltitrexed) as the standard for first-line therapy of patients with MPM [17]. After failure of the first-line chemotherapy, no standard treatment has been defined and best supportive care is generally applied to the patients with MPM [17]. However, there are a growing number of patients who are still fit to receive the second-line treatment.

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Even with the current standard of care, the prognosis of patients with MPM remains to be dismal, with a median survival of approximately 1 year. Therefore, new agents are needed to treat this disease and clinical research efforts should focus on more efficient first-line treatments and on active second-line therapies for patients with MPM. During the last decade, a number of targeted agents have been developed in oncology. The aim of this review is to summarize the literature on targeted therapies that have been specifically assessed in MPM.

## Methods

A comprehensive review of MPM-targeted therapy literature was carried out. The PubMed database was searched for publications dated from January 2000 to May 2010 having the keywords 'mesothelioma', 'therapeutics,' and 'drug therapy'. These keywords were used in various combinations as medical subject headings and as text words. The literature search was limited to clinical trials. Abstracts from the Annual Meetings of the American Society of Clinical Oncology (ASCO) and the American Thoracic Society (2006–2010), the 31st and 32nd Congresses of the European Society of Medical Oncology (2006 and 2008), the 12th and 13th World Conferences on Lung Cancer (2007 and 2009), the ninth International Conference of the International Mesothelioma Interest Group (2008), and the 2009 Annual Meeting of the European Respiratory Society were also reviewed. Ongoing clinical trials were searched using the website *www.clinicaltrials.gov*.

## Results

The literature search identified 135 articles that may have been relevant to this review. The manual selection of these articles retained 11 clinical trials. In addition, 12 communications were identified from recent international meetings.

For the sake of clarity, results of this search were classified according to the proposed classification of different cancer cell pathways [18].

### Cancer cell growth pathways

Schematically, cell growth signaling can be divided into three distinct, though closely connected parts. First, there are the upstream growth factors and their receptors at the cell membrane. From there, molecular mechanisms of signal transduction and intracellular messengers form a relay informing the nucleus of the given stimulus. Finally, an effector pathway leads the cell eventually to cell division and proliferation.

#### *Cell membrane receptors*

Epidermal growth factor receptor (EGFR) expression was detected by immunohistochemistry in 68% of mesothelioma specimens, with a higher incidence in epithelioid subtypes (88% in epithelioid subtypes vs. 50% in other subtypes) [19]. For this reason, EGFR expression is not an independent prognostic factor in MPM [20]. Treatment of mesothelioma cell lines with the EGFR tyrosine kinase inhibitor (TKI), gefitinib, resulted in the inhibition of EGFR-dependent cell signaling and significant dose-dependent reduction of colony formation [21]. From those preclinical data, a phase II study of gefitinib in the patients with MPM who were untreated earlier was conducted by the Cancer and Leukemia Group B [22]. According to Response Evaluation Criteria in Solid Tumors, an objective response was observed in two patients (4%), and stable disease in 21 patients (49%; Table 1). The researchers hypothesized that EGFR overexpression in tumor could predict gefitinib efficacy, but EGFR immunohistochemical expression in MPM samples was not associated with disease control. Median failure-free survival was similar for patients with low EGFR-expressing tumors and for those with high EGFR-expressing tumors (2.7 months in both groups) [22]. Erlotinib, another EGFR TKI, was administered in 63 chemotherapy-naive patients with MPM in a phase II study [23]. Among the 33 patients with measurable disease, no objective response was seen, and 14 patients experienced stable disease (42%; Table 1). The immunohistochemical expression of several biomarkers, known to be involved in the EGFR signaling pathway, was assessed in tumor samples: EGFR, human epidermal growth factor receptor 2, phosphatase and tensin homolog, and phosphorylated forms of EGFR, extracellular signal-regulated protein kinase, AKT, mammalian target of rapamycin, and two other proteins. No significant correlation was shown between disease control by erlotinib and expression of any of these biomarkers [23]. Finally, in a phase II trial of erlotinib and bevacizumab [a recombinant humanized

**Table 1 Epidermal growth factor receptor and platelet-derived growth factor receptor tyrosine kinase inhibitors in malignant pleural mesothelioma**

| Author (reference) | Agent | Patients | No. | RR (%) | DCR (%) | mPFS (mo) (95% CI) | mOS (mo) (95% CI) |
|---|---|---|---|---|---|---|---|
| Govindan *et al.* [22] | Gefitinib | Untreated earlier | 43 | 4 | 53 | 2.6 (1.5–4.2) | 6.8 (3.5–10.3) |
| Garland *et al.* [23] | Erlotinib | Untreated earlier | 63 | 0 | 42 | 2 (2–4) | 10 (5–13) |
| Jackman *et al.* [24] | Erlotinib + beacizumab | Previously treated (88%) | 24 | 0 | 50 | 2.2 (1.4–5.9) | 5.8 (2.8–10.1) |
| Mathy *et al.* [25] | Imatinib | Untreated earlier (92%) | 25 | 0 | NR | NR | 13.1 (NR) |
| Porta *et al.* [26] | Imatinib | Treated earlier (82%) | 11 | 0 | 36 | 1.8 (NR) | 4.6 (NR) |
| Dudek *et al.* [27] | Dasatinib | Treated earlier | 46 | 2 | 25 | 2.1 (1.8–3.8) | 6 (4.3–7.8) |

CI, confidence interval; DCR, disease control rate (complete response + partial response + stable disease); mo, months; mOS, médian overall survival; mPFS, median progression-free survival; No., number of patients; NR, not reported; RR, response rate (complete response + partial response).

antibody directed to vascular endothelial growth factor (VEGF)] in the patients with MPM who had progressed after one earlier chemotherapy regimen, there was no objective response; stable disease was achieved in 50% of the patients, and median time to progression was only 2.2 months (Table 1) [24]. The minimal activity of EGFR TKI in MPM might be explained by the fact that EGFR activating mutations confer greater efficacy to these agents in non-small-cell lung cancer are uncommon in MPM [28]. To date, the activity of monoclonal antibodies directed toward EGFR, such as cetuximab or panitumumab, has not been assessed in MPM.

Although the platelet-derived growth factor (PDGF) receptor was thought to play a pivotal role in mesothelioma oncogenesis, there were no objective responses in single-agent phase II trials of the PDGF inhibitor, imatinib (targeting also c-Kit and BCR-Abl) (Table 1) [25,26]. A combination of imatinib with cisplatin and pemetrexed is currently under investigation in chemotherapy-naive patients with MPM (NCT00402766). In addition, recent in-vitro data suggesting that imatinib enhanced the therapeutic effects of gemcitabine in mesothelioma xenografts [29] has led to an ongoing phase II trial of this combination in refractory patients with MPM (NCT00551252).

Dasatinib is an oral, potent adenosine triphosphate-competitive inhibitor of multiple tyrosine kinases including BCR-Abl, c-kit, PDGF, and Src family kinases. This drug was administered in 46 patients with MPM, earlier treated with one pemetrexed-based regimen, in a phase II study. At the 2010 ASCO meeting, Dudek *et al.* [27] reported that the initial dose of 70 mg, (twice daily) had to be reduced to 50 mg (twice daily) as 50% of the 12 first patients enrolled had adverse events of more than or equal to grade 3. During the study, three patients experienced grade 5 toxicities. With regard to the clinical activity of dasatinib, a partial response was observed in one patient (2%), and only 23% of the patients achieved stable disease (Table 1). The median progression-free survival (PFS) was 2.1 months, and the median OS was 6 months [27].

In summary, phase II studies of TKIs directed against the EGF and the PDGF receptors failed to show significant clinical activity in MPM.

#### *Nuclear targets*

Histones play a central role in gene transcription regulation. Epigenetic regulation of tumor suppressor genes through chromatin condensation and decondensation can lead to tumorogenesis. A family of histone acetyltransferases and deacetylases regulates this process. Histone deacetylases (HDACs) facilitate chromatin condensation, thus preventing gene transcription, resulting in the loss of heterozygosity of the tumor suppressor genes, therefore leading to cell cycle progression and unchecked growth. HDAC inhibitors (HDACIs) are agents that prevent deacetylation and reinstate control over the cell cycle. Preclinical studies, extensively reviewed by Paik and Krug [30], have shown activity of HDACIs in MPM. Suberoylanilide hydroxamic acid, or vorinostat, an oral HDACI (with specificity against classes I, II, and IV HDACs), was studied in an early phase I trial that included 13 patients with mesothelioma [31]. Among them, two and six patients experienced a partial response and a stable disease, respectively. Consequently, a randomized, placebo-controlled phase III study of vorinostat in the patients with MPM was initiated (NCT00128102). This ongoing study plans to accrue 660 patients with MPM for whom treatment with pemetrexed and platinum has failed. The trial continues after two interim analyses. Belinostat (PXD101) is another HDACI with similar specificity against HDACs classes, but five times more biological activity than vorinostat in preclinical studies [32]. However, in a phase II study in pretreated patients with MPM, no objective response was observed and only 15% of the patients experienced disease stabilization [33]. There is a scientific rationale to combine HDACIs with conventional cytotoxic agents. In a phase I trial of vorinostat in combination with cisplatin and pemetrexed in advanced solid tumors, stable disease was observed in 58% of patients, including three of five patients with MPM enrolled in this study [34]. In a phase II study, valproate acid was combined with doxorubicin in patients with MPM who were treated earlier [35]. Indeed, in-vitro data suggested that valproate acid had an inhibitory effect on classes I and IIa HDACs, had a pro-apoptotic effect on MPM cell lines and synergized with doxorubicin to induce apoptosis in these cell lines. In this study, the response rate was 16%, the median PFS was 2.5 months and the median OS was 6.7 months [35].

In summary, HDACIs might be a relevant therapeutic strategy in MPM. Results from phase III trials are now awaited.

Ranpirnase is a ribonuclease enzyme that specifically targets and degrades tumor cell tRNA and therefore inhibits protein synthesis, resulting in cell cycle arrest at the G1 phase. In a phase II MPM trial, single-agent ranpirnase resulted in a 5% response rate, a 46% stable disease rate, and a median OS of 6 months [36]. A small phase III trial compared ranpirnase with doxorubicin in patients with unresectable MPM and showed no statistically significant difference in OS (median OS 7.7 vs. 8.2 months) [37]. Recently, the results of a large multicenter phase III trial comparing doxorubicin with the combination of doxorubicin and ranpirnase in the patients with MPM (both chemotherapy-naive and treated earlier with one chemotherapy regimen) were reported [38]. Tumor response evaluation as assessed by investigators was in favor of the combination arm (tumor regression: 28 vs. 18%, tumor stabilization: 47 vs. 47%, $P = 0.04$). In the overall population, there was no

significant difference in OS [11.1 vs. 10.7 months; hazards ratio (HR) 1.02, 95% confidence interval (CI): 0.82–1.26] whereas a preplanned subgroup analysis including 130 pretreated patients with MPM showed a significant advantage in survival in favor of the combination arm (10.5 vs. 9 months; HR: 1.49, 95% CI: 1.02–2.17). However, further development of ranpirnase is uncertain.

### Angiogenesis

The potential role of anti-angiogenic agents in mesothelioma is under investigation. Indeed, MPM is a disease characterized by a sustained angiogenesis and an increased vessel density has been correlated with a worse outcome [39]. Preclinical studies detected VEGF and its receptors, VEGFR1 and VEGFR2, in a majority of mesothelioma cell lines and tumor specimens [40–42]. Moreover, recombinant human VEGF has been found to stimulate the proliferation of mesothelioma cells *in vitro*, and this growth could be inhibited by the use of neutralizing antibodies against either VEGF or its receptors [42]. Compared with nonmalignant pleural disease patients, patients with MPM were found to have higher levels of VEGF in pleural fluid [42] and in serum [43]. Serum concentrations of VEGF were inversely correlated with the survival of patients with MPM, but this was not confirmed by multivariate analysis [42,43]. In tumor tissue, VEGF immunohistochemical expression was reported as an independent prognostic factor [44].

Angiogenic inhibition with bevacizumab, a monoclonal humanized antibody directed against VEGF, provided a significant survival benefit in colorectal, non-small-cell lung, breast and renal cell carcinomas [45–49]. In chemotherapy-naive patients with MPM, a randomized phase II trial using cisplatin and gemcitabine with bevacizumab (15 mg/kg) or placebo did not show any improvement in the response rate (25 vs. 22%) nor survival (HR: 0.93, $P = 0.88$) in the experimental arm (Table 2) [50]. However, the choice of chemotherapy agent (gemcitabine) was not optimal. In a subgroup analysis, the investigators reported that patients with serum VEGF concentrations above the median value at baseline experienced a shorter PFS ($P = 0.02$) and OS ($P = 0.007$) [50]. Moreover, in patients with serum VEGF concentrations below the median value at baseline, PFS ($P = 0.043$) and OS ($P = 0.028$) were greater for patients treated with bevacizumab [50], suggesting that antiangiogenic therapy could benefit some selected patients with MPM. Several ongoing studies are evaluating bevacizumab with pemetrexed and cisplatin (NCT00295503, NCT00651456) or carboplatin (NCT00407459, NCT00604461). Recently, preliminary results of an open-label phase II study (NCT00295503) combining cisplatin, pemetrexed, and bevacizumab (15 mg/kg) as a first-line regimen for mesothelioma were presented [51]. At the time of analysis, 40 patients with pleural, but also peritoneal or testicular mesothelioma had been enrolled. The response rate was 43% and an additional rate of stable disease was observed in 38% of the patients (Table 2). The median PFS and OS were 6.9 and 14.8 months, respectively. At the 2010 ASCO meeting, preliminary results of an ongoing randomized phase II–III studies (NCT00651456) were presented [52]. In this trial, chemotherapy-naive patients with MPM are randomized between standard chemotherapy with cisplatin and pemetrexed versus the same standard chemotherapy and bevacizumab (15 mg/kg). There were no major differences in toxicity between the two arms. Among the 93 patients assessable at 6 months post-randomization, disease control rate was achieved in 57.4% of patients in the bevacizumab arm compared with 45.7% of patients in the control arm (Table 2). As the phase II part of this study met its primary endpoint, the phase III part of the trial has started in June 2010.

Thalidomide, a drug used earlier as a sedative, especially during pregnancy and abandoned because of its teratogenic effects, has recently been revisited in oncology for its antiangiogenic properties [60–65]. In an open-label phase II study, the single agent, thalidomide, was reported to achieve disease stabilization in 27.5% of patients with MPM (both chemotherapy-naive and pretreated)

**Table 2 Antiangiogenic agents in malignant pleural mesothelioma**

| Author (reference) | Agent | Patients | No. | RR (%) | DCR (%) | mPFS (mo) (95% CI) | mOS (mo) (95% CI) |
|---|---|---|---|---|---|---|---|
| Karrison *et al.* [50] | Cis + Gem + placebo | Untreated earlier | 55 | 22 | 82 | 6 (NR) | 14.7 (NR) |
| | Cis + Gem + bevacizumab | Untreated earlier | 53 | 25 | 76 | 6.9 (NR) | 15.6 (NR) |
| Dowell *et al.* [51] | Cis + Pem + bevacizumab | Untreated earlier | 40 | 43 | 81 | 6.9 (5.3–7.7) | 14.8 (10–18.8) |
| Zalcman *et al.* [52] | Cis + Pem | Untreated earlier | 46 | 35[a] | 46[a] | NR | NR |
| | Cis + Pem + bevacizumab | Untreated earlier | 47 | 38[a] | 57[a] | NR | NR |
| Baas *et al.* [53] | Thalidomide | Untreated earlier (53%) | 40 | NR | 28[a] | NR | 7.6 (4.3–10.8) |
| Jahan *et al.* [54] | Vatalanib | Untreated earlier | 47 | 11 | 77 | 4.1 (NR) | 10 (NR) |
| Nowak *et al.* [55] | Sunitinib | Treated earlier | 51 | 10 | 75 | 3.4 (NR) | 6.7 (NR) |
| Janne *et al.* [56] | Sorafenib | Untreated earlier (61%) | 47 | 4 | 64 | 3.7 (NR) | 10.7 (NR) |
| Irshad *et al.* [57] | Sorafenib | Treated earlier | 18 | 11 | 83 | 3.7 (NR) | NR |
| Garland *et al.* [58] | Cediranib | Treated earlier | 45 | 9 | 42 | 3 (NR) | 10 (NR) |
| Gregorc *et al.* [59] | NGR–hTNF | Treated earlier | 57 | 2 | 46 | 2.8 (2.2–3.3) | 12.1 (7.2–17) |

95% CI, 95% confidence interval; Cis, cisplatin; DCR, disease control rate (complete response + partial response + stable disease); Gem, gemcitabine; mo, months; mOS, médian overall survival; mPFS, median progression-free survival; No, number of patients; NGR–hTNF, asparagine–glycine–arginine–human tumor necrosis factor; NR, not reported; Pem, pemetrexed; RR, response rate (complete response + partial response).
[a]At 6 months.

for more than 6 months (Table 2) [53]. However, the toxicity profile of the drug limited the intensity of the treatment dose.

Multitargeted TKIs with anti-VEGF activity have also been investigated in MPM. In a phase II trial in the patients with MPM who were untreated earlier, vatalanib (PTK787/ZK 222584), an oral anilinophthalazine that targets VEGFR1-3, PDGFR-β, and c-Kit, showed an 11% response rate, a 66% stable disease rate, a median PFS of 4.1 months, and a median OS of 10 months (Table 2) [54]. However, the 3-month PFS rate (55%) did not meet the prespecified primary endpoint of 75%.

Sunitinib (SU11248), an oral agent targeting VEGFR1-3, PDGFR, c-Kit, and Flt-3, was evaluated in a single-arm phase II trial in patients who had experienced treatment failure with a one platinum and antimetabolite regimen [66,67]. In this study, an objective response was defined by either modified Response Evaluation Criteria in Solid Tumors on a CT scan or metabolic response on fluorodeoxyglucose positron emission tomography in patients without earlier talc pleurodesis. Final results were presented at the 2010 ASCO meeting [55]. The protocol-defined response rate was 22%, the median time to progression was 3.4 months, and the median OS was 6.7 months (Table 2). Toxicity was relatively high, with 21% of grade 3 fatigue, one grade 4 pneumonitis, one possible treatment-related death from pulmonary infiltrates and respiratory failure, and four patients who developed pleural effusions or ascites without radiological evidence of progressive disease.

A phase II trial using sorafenib (BAY 43-9006), an oral TKI-targeting VEGFR2-3, PDGFR-β, B-Raf, and c-Raf, in the patients with MPM (both chemotherapy-naive and treated earlier with pemetrexed) found a 4% overall response rate, a 60% stable disease rate, a median failure-free survival of 3.7 months, and median OS of 10.7 months (Table 2) [56]. Chemotherapy-naive patients had worse survival outcomes than the patients who were treated earlier, possibly because of patient selection. A second phase II trial was specifically conducted in mesothelioma patients who had earlier received platinum combination chemotherapy, and the results were recently presented [57]. Partial response and stable disease were observed in 11 and 72% of the patients, respectively (Table 2). This trial met its primary endpoint, with a PFS rate at 24 weeks of 38% patients. In both sorafenib studies, the toxicities were mild and easily manageable.

Cediranib (AZD2171), another multitargeted TKI with potent activity against VEGFR1-3 and lesser activity against PDGFR-β and c-Kit, was assessed in pretreated patients with MPM (Southwest Oncology Group, S0509 phase II study) [58]. Among the 45 eligible patients, tumor response and stable disease were observed in 9 and 33% of the patients, respectively (Table 2). Median PFS was estimated at 3 months, and median OS at 10 months. On the basis of these data, a randomized study combining pemetrexed and cisplatin with cediranib or placebo in the first-line setting is ongoing (NCT01064648).

Pazopanib (GW786034), a second-generation multitargeted TKI against VEGFR1-3, PDGFR-α-β, and c-Kit, is currently under investigation in MPM (NCT00459862).

Alternatively, a ligand-directed vascular-targeting approach was explored in second-line MPM with asparagine–glycine–arginine–human tumor necrosis factor (NGR–hTNF), which consists of hTNF fused to the cyclic tumor-homing peptide, NGR, that is able to selectively bind an aminopeptidase N isoform overexpressed on tumor blood vessels [59]. In this phase II study, NGR–hTNF (0.8 μg/m$^2$) was given intravenously every 3 weeks in 43 patients with MPM, and a subsequent cohort of 14 patients received the drug at the dose on a weekly basis. In the overall population, 46% of patients achieved disease control (partial response, 2%; stable disease, 44%), the median PFS was 2.8 months and the median OS was 12.1 months (Table 2).

In summary, several antiangiogenic agents have been assessed in MPM clinical studies. Among these agents, bevacizumab is the most advanced in development, with an ongoing phase III trial in the first-line setting. In addition, some multitargeted TKIs with anti-VEGF activity, notably sorafenib, showed clinical activity in phase II studies.

## Apoptosis

Proteasome complexes degrade ubiquitinated proteins and play a central role in the regulation of a wide variety of proteins involved in apoptosis, such as cyclins, cyclin-dependent kinases and cyclin-dependent kinase inhibitors, c-Myc, or nuclear factor-κB. Bortezomib (PS-341) is a potent and selective proteasome inhibitor, already approved for the management of multiple myeloma. Preclinical studies in cell lines and murine xenograft models showed that bortezomib had an antitumor activity against MPM [68,69]. Three clinical phase II trials are under way testing bortezomib in combination with cisplatin (NCT00458913), oxaliplatin (NCT00996385) and in monotherapy (NCT00513877) in the patients with MPM.

## Conclusion

The need for more effective treatments for the patients with MPM is obvious. However, drug development in MPM strikes against several issues. In phase II cancer clinical trials, the biological antitumor activity of drugs is generally assessed by measuring tumor shrinkage and the primary endpoint is classically the response rate. This endpoint may not be the most appropriate in the particular case of MPM. On account of its unique pattern of growth, the response criteria have always been difficult to apply to MPM [70]. Moreover, new drugs and notably

targeted therapies are often more likely to work as cytostatic than cytotoxic agents. From this perspective, some researchers proposed replacing the response rate by the PFS rate at a fixed time point as the primary end point in MPM phase II studies [71]. In addition, radiological response using a CT scan does not necessarily correlate with clinical benefit. However, no metabolic imaging technique has been validated in MPM as a surrogate for survival and no biological marker has been unequivocally shown to be predictive of clinical outcome [72].

To date, several targeted agents have been assessed in MPM. Although TKIs directed against the EGF and the PDGR receptors did not show significant clinical activity in phase II studies, some other targeted therapies seemed to be promising, notably HDACI and antiangiogenic agents. However, none of these agents has yet reached daily practice. Hopefully, the results of ongoing clinical studies will show a significant benefit and will change the current standard of care in MPM. In parallel, efforts must continue in the area of translational research for MPM.

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