Treatment of malignant pleural mesothelioma: current status and future directions

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Malignant pleural mesothelioma (MPM) is an aggressive tumor, with a poor prognosis and an increasing incidence as a result of widespread exposure to asbestos. Approximately 80% of MPM can be attributed to asbestos fiber exposure. Surgery and radiotherapy have a limited role in highly selected patients and systemic therapy is the only potential treatment option for the majority of patients. Unfortunately, despite some definite activity of the novel antifolates such as pemetrexed and raltitrexed, the results even in combination with platinating agents are still modest. The median survival of these patients remains of approximately 1 year. Improvements in surgical and radiotherapy techniques, in tumor assessment and staging and in the knowledge of the major molecular pathways involved in MPM are needed to increase the survival of these patients.

Keywords: diagnosis • malignant pleural mesothelioma • multimodality approach • pathogenesis • prognosis • treatment

Malignant pleural mesothelioma (MPM), the most common primary tumor of the pleura, is an aggressive tumor with a poor prognosis and a median survival of approximately 12 months. MPM is a rare disease, but its incidence has been increasing in several countries as a result of widespread exposure to asbestos, and it is predicted to peak in the next 10–15 years [1], especially in the developing countries where use of asbestos has not yet been banned [2]. Although the mechanism of carcinogenesis is not fully understood, approximately 80% of MPM can be attributed to asbestos fiber exposure. The other potential carcinogenic factors are exposure to simian virus 40, radiation and erionite [3].

The management of patients with MPM is controversial [4]. A difficulty in diagnosing and staging the disease, especially in its early stages, has hindered the development of a generally accepted stage-related approach. Moreover, MPM is a heterogeneous disease with a variable clinical course. A number of prognostic factors have been described and two major prognostic scoring systems have been proposed [5,6]. The majority of patients (80%) are diagnosed in stage III/IV [7] and these patients are not amenable to radical surgery with extrapleural pneumonectomy (EPP). Improvements in surgical approaches, postoperative care and new radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT), have increased the number of patients that could be candidate to locoregional treatment, reducing morbidity and mortality rates [8,9]. However, systemic therapy is the only treatment option for the majority of these patients, but their poor performance status and the low chemo- and radiosensitivity of this tumor reduce attempts at medical interventions [10]. Furthermore, the relatively low incidence of the disease has made it difficult to conduct randomized controlled trials with an adequate number of cases.

Presently, the combination of antimetabolites plus platinum compounds is considered the standard of care as a front-line chemotherapy in MPM patients because it was shown to significantly improve response rates (RRs), time to

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progression (TTP), overall survival (OS) and quality of life [11]. Unfortunately, all MPM patients progress after first-line treatment. Second-line chemotherapy is being increasingly used in the clinical practice, because patients are frequently still healthy at the time of disease progression. Until recently, most MPM chemotherapy trials have focused on chemo-naive patients, with few providing results to guide decisions regarding second-line therapy [12].

Nevertheless, advances in the understanding of the molecular biology of MPM have identified promising new candidates for targeted treatments [13–15]. Consequently, several biological agents have been explored or are currently under evaluation.

This review summarizes the current management of MPM and outlines the therapeutic approaches in development.

Current management Diagnosis & staging

Correlation between clinical, imaging, and pathological findings is critical to a correct and rapid diagnosis. However, difficulty in diagnosing and staging the disease, especially in its early stages, has thwarted the development of a generally accepted stage-related approach.

Malignant mesothelioma can be referred to three principal histological types: epithelial, sarcomatoid and mixed (or biphasic). MPMs are exclusively epithelial in approximately 50-67% of cases, sarcomatoid in 7-21% and mixed in 24-35% [16]. In order to obtain adequate tissue for histologic diagnosis and to facilitate staging, the investigation of choice is a thoracoscopic examination, by which excessive fluid can be drained, followed by pleurodesis. Thoracoscopy yields a diagnosis in at least 80% of patients without committing the patient to a major surgical procedure [17]. The major difficulty in MPM diagnosis is the differential diagnosis between MPM and lung cancer. MPM do not stain with carcinoembryonic antigen and thyroid transcription factor-1, both of which are typically positive in adenocarcinomas [18]. The immunohistochemical staining for epithelial membrane antigen, the calciumbinding protein calretinin, Wilm's tumor 1 antigen, cytokeratin 5/6, HBME-1 or mesothelin are useful in identifying MPM. 9p21 (locus harboring the p16 gene) homozygous deletion assessed by FISH on paraffinembedded tissue may be very useful for differentiating MPM from reactive mesothelial hyperplasia [19]. The rate of deletion of the 9p21 is approximately 60% of all cases of MPM [20]. Furthermore, immunostaining pattern for membranous podoplanin immunoreactivity, in conjunction with calretinin, would be more specific than CK5/6 and Wilm's tumor 1 in differentiating

epithelioid malignant mesothelioma from primary neoplasm of the lung, breast, and ovary [21]. Finally, the commercial FISH-test UroVysion test, originally designed for the cytological diagnosis of bladder cancer, can be used to accurately distinguish malignant and reactive cells in effusions, particularly when cytology is inconclusive [22].

A correct staging is mandatory in the treatment of MPM. CT and PET scan should be considered as complementary to define the extent of disease, selecting the optimal patients for a multimodality approach and to assess the response to treatment. CT scan is currently the most accurate noninvasive method to stage patients, to assess response to treatment and to detect recurrent disease postoperatively, but it is often inaccurate in diagnosing chest wall involvement or extension through the diaphragm. A study comparing CT scan and MRI for preoperative staging showed that MRI is not significantly better than CT scan in defining the local extent of the tumor [23]. The use of ¹⁸F-fluorodeoxyglucose (FDG) PET for the diagnosis of MPM has been described recently. In one study of 65 MPM patients, this imaging technique correctly detected extrathoracic metastases but failed to reliably identify the locoregional (tumor and mediastinal nodal) status of MPM [24]. Integrated CT-PET with coregistration of anatomic and functional imaging data increases the accuracy of MPM staging for T4 disease (sensitivity 67%, specificity 93%), while it remains inaccurate in the evaluation of nodal metastases (sensitivity 38%, specificity 78%) [25,26].

At present, the recommended classification for clinical use is the International Mesothelioma Interest Group Classification [27], which is mainly surgical-pathological and may not be completely applicable to cross-sectional imaging and to the complex lymphatic drainage of the pleura [28,29]. The distinction between N1, N2 and N3 nodes is currently preserved in this staging system in order to facilitate further studies of the prognostic implications of nodal metastasis (Tables 1 & 2).

Prognosis

The median survival of patients with MPM is 12 months, ranging from 8 months for stage IV patients to 40 months for stage I [30]. The clinical course of these patients varies widely, ranging from slowly progressive to more aggressive disease. Two prognostic scoring systems have been devised (Table 3). Poor prognosis was associated with a poor performance status (according to Eastern Cooperative Oncology Group or Karnofsky scores), a high white cell count, a probable/possible histologic diagnosis of MPM, male gender and having sarcomatous tissue as the histologic subtype. Taking these five factors into

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Table 1. International staging developed by the International Mesothelioma Interest Group: descriptor characterization.				
Descriptor	Region involved	Characteristics		
Tla	Limited to the ipsilateral parietal pleura, including the mediastinal and diaphragmatic pleurae	No involvement of the visceral pleura		
T1b	Ipsilateral parietal pleura, including the mediastinal and diaphragmatic pleurae	Scattered tumor foci that also involve the visceral pleura		
Т2	Each ipsilateral pleural surface	 At least one of the following: Involvement of the diaphragmatic muscle A confluent visceral pleural tumor (including fissures) or tumor extension from the visceral pleura into the underlying pulmonary parenchyma 		
Т3	Locally advanced but potentially resected tumor (each ipsilateral pleural surface)	 At least one of the following: Involvement of the endothoracic fascia Extension into mediastinal fat A solitary, completely resectable focus of tumor that extends into the soft tissues of the chest wall Nontransmural involvement of the pericardium 		
Τ4	Locally advanced, technically unresectable tumor (each ipsilateral pleural surface)	 At least one of the following: Diffuse tumor extension or multiple tumor foci in the chest wall with or without associated rib destruction Direct transdiaphragmatic extension to the peritoneum Direct extension to the contralateral pleura Direct extension to the mediastinal organs Direct extension to the spine Extension to the internal surface of the pericardium with or without pericardial effusion or involvement of the myocardium 		
NX		Regional lymph nodes not assessable		
N0		No regional lymph node metastases		
N1		Metastases in ipsilateral bronchopulmonary or hilar lymph nodes		
N2		Metastases in subcarinal or ipsilateral mediastinal lymph nodes, including ipsilateral internal mammary lymph nodes		
N3		Metastases in contralateral mediastinal, contralateral internal mammary, and ipsilateral or contralateral supraclavicular lymph nodes		
MX		Distant metastases not accessible		
M0		No distant metastases		
M1		Distant metastases		

Table 2. International staging developed by the International Mesothelioma Interest Group: stage and corresponding tumor, node and metastasis.			
Stage	Tumor	Node	Metastasis
Ia	T1a	N0	M0
Ib	T1b	N0	M0
II	Т2	N0	M0
III	Any T3	Any N1 or N2	M0
IV	Any T4	Any N3	M1

consideration, patients were classified by the European Organisation for Research and Treatment of Cancer into two groups: a good-prognosis group (1-year survival rate: 40%) and a poor-prognosis group (1-year

survival 12%) [5]. Female gender was strongly associated with a better OS rate (p < 0.001) and the effect of gender on OS did not seem to be related merely to the fact that the majority of female patients had

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Table 3. European Organization for Research and Treatment of Cancer and Cancer and Leukemia Group B prognostic scoring systems.					
Group	Description	Medium survival (months; 95% CI)	1-year survival (%; 95% CI)	2-year survival (%; 95% CI)	Ref.
EORTC					
Low risk (score ≤1.27)	WBC >8.3 × 10^{9} /l (score: +0.55) PS: 1 or 2 (score: +0.60) Histologic diagnosis (score: +0.52) Sarcomatoid histological subtype (score: +0.67) Male gender (score: +0.60)	10.8	40 (30–50)	14 (CI 6–22)	[5]
High risk (score >1.27)	WBC >8.3 × 10^9 /l (score: +0.55) PS: 1 or 2 (score: +0.60) Histologic diagnosis (score: +0.52) Sarcomatoid histological subtype (score: +0.67) Male gender (score: +0.60)	5.5	12 (4–20)	0	
CALGB					
1	PS: 0, age <49 years PS: 0, age ≥49 years, HGB ≥14.6 g/dl	13.9 (11.1–31.4)	63 (46–77)	38 (23–55)	[6]
2	PS: 1/2, WBC <8.7 \times 10 ⁹ /l, no chest pain	9.5 (6.9–14.7)	41 (26–57)	21 (10-37)	
3	PS: 0, age \geq 49 years, HGB <14.6 g\dl PS: 1/2, WBC <15.6 × 10 ⁹ /l, chest pain, no weight loss, HGB \geq 12.3 g/dl PS: 1/2, 9.8 \leq WBC <15.6 × 10 ⁹ /l, chest pain, weight loss, HGB \geq 11.2 g/dl	9.2 (7.5–10.5)	30 (23–37)	10 (6–16)	
4	PS: 1/2, 8.7 \leq WBC <15.6 \times 10 $^{9}/I$, no chest pain	6.5 (3.7–9.4)	25 (14–42)	6 (2–17)	
5	PS: 1/2, WBC <15.6 \times 10 ⁹ /l, chest pain, no weight loss, HGB <12.3 g/dl PS: 1/2, 9.8 \leq WBC <15.6 \times 10 ⁹ /l, chest pain, weight loss, HGB <11.2 g/dl PS: 1/2, WBC <9.8 \times 10 ⁹ /l, chest pain, weight loss	4.4 (3.4–5.1)	7 (3–15)	0	
6	PS: 1/2, WBC ≥15.6 × 10 ⁹ /I	1.4 (0.5–0.36)	0	0	
CALGB: Cancer and Leukemia Group B; EORTC: European Organization for Research and Treatment of Cancer; HGB: Hemoglobin; PS: Performance status (Eastern Cooperative Oncology Group); WBC: White blood cells.					

pure epithelial tumors [31]. Immunohistochemical analysis revealed intense nuclear ERB staining in normal pleura that was reduced in tumor tissues. Conversely, neither tumors nor normal pleura stained positive for ERa. Multivariate analysis of 78 MPM indicated that ERβ expression is an independent prognostic factor of better survival. Preclinical data supports the hypothesis that ER β acting as a tumor suppressor is of high potential relevance to prediction of disease progression and to therapeutic response of MPM patients [32]. The Cancer and Leukemia Group B has reported that the key prognostic factors in MPM include performance status, age, hemoglobin, white blood cell count, chest pain and weight loss, and that these may be useful in predicting outcomes for chemotherapy-treated patients. As performance status, age and white blood cell count increase, survival decreases [6]. Prospective validation of these prognostic groupings and, in particular, the worst prognostic Cancer and Leukemia Group B cohorts has been reported [33].

Treatment

Surgery

The role of surgery in MPM is still controversial and the optimal procedure for resection is not standardized. Its results are difficult to interpret because of the relatively small number of patients, the variable patient selection, the lack of randomized trials, and often the addition of another treatment modality to surgery. In general, patients with stage I disease can be considered candidates for radical surgery. Pleurectomy/decortication (P/D) and EPP are the two major types of operation. EPP involves an en bloc resection of lung, pleura, pericardium and diaphragm, while P/D involves resection

of the parietal and visceral pleurae and the pericardium and diaphragm when necessary, but spares the lung. Both EPP and P/D are cytoreductive treatment options with the aim to remove all gross disease and to achieve macroscopic complete resection [34]. Despite a heightened interest in EPP over the past decade, concerns about the morbidity and mortality of this surgical procedure, and its efficacy, have delayed a consensus in its practice. In addition, there is a lack of robust clinical data on prognostic factors for OS and quality of life evaluation. To date, no randomized controlled trials have been conducted to examine the potential benefits of EPP. As macroscopic incomplete R2-resection is associated with increased mortality, the similar performance of P/D and EPP in achieving R0/R1 resection is of critical importance [35]. Originally P/D was a palliative option for controlling pleural effusion [36]. Recently, lung-sparing surgery for MPM seems to be an alternative for patients unsuitable to undergo EPP, depending on co-morbidities, stage of disease and histology. EPP is a rather complex operation, which should be performed by skilled surgeons and in selected centers. The operative mortality is 5–9%, but morbidity is approximately 25%. P/D has the advantage of limiting the procedure related morbidity, thus allowing patients to maintain physiological reserve, and is applicable in all stages and all types of histology. Indeed, advanced disease was associated with poorer survival, but performing EPP in advanced stages of MPM did not lead to superior survival. In a recent retrospective analysis, Flores and colleagues investigated the outcomes of EPP and P/D, with OS as the primary end point, observing that patients who underwent P/D had a better survival than those who underwent EPP. However, the authors suggested that the reasons are multifactorial and subject to selection bias and the choice of resection should be tailored to the extent of disease, patient comorbidities, and type of multimodality therapy planned [30]. The ongoing randomized Mesothelioma And Radical Surgery (MARS) trial in the UK is attempting to determine the benefit of surgery in the treatment of mesothelioma. In this study, 50/112 (45%) of patients entering the evaluation and induction phase of the trial went on to be randomized. The authors have shown that this randomization between surgery and no surgery is feasible [37].

Surgery alone has not been extensively tested yet, and the use of combined modality approaches has been better investigated.

Radiotherapy

The role of radiation therapy (RT) in the management of MPM is still debated and RT alone has probably no major role in disease control and survival. RT is often used for palliation of pain, and it has often been added to surgery in an attempt to improve local control and reduce local failure.

Adjuvant hemithoracic RT was studied as a way of improving local control after EPP, especially because a higher dose of radiation can be achieved without risk of pneumonitis, as the lung has been removed. Memorial Sloan-Kettering Cancer Center investigators conducted a prospective trial in which 54 patients underwent EPP followed by RT (54 Gy). This therapeutic approach resulted in a dramatic reduction in local relapse and prolonged survival in patients with early-stage disease [38]. However, the diffuse nature of the tumor, which often covers most of the lung and the interlobular fissures, is the principal limitation to radiotherapy. The recent improvements in radiation treatment techniques, such as IMRT, have provided the potential to conform radiation doses tightly to target volumes reducing normal tissue toxicity. Ahamad and colleagues showed how IMRT after EPP was feasible, with modest toxicity and excellent local control [39]. There is a report of severe toxicities attributable to IMRT after EPP. This report raised serious safety concerns and has resulted in a much more cautious exploration of IMRT techniques in this patient population. In particular, the authors recognized the acute respiratory distress syndrome as a combined modality toxicity, which underscores the lowered pulmonary reserves of patients who undergo trimodality treatment [40]. Furthermore, RapidArc (RA) demonstrated, compared with conventional IMRT, similar target coverage and better dose sparing to the organs at risk. The number of monitor units and the time required to deliver a 2-Gy fraction were much lower for RA, allowing the possibility to incorporate this technique in the treatment options for mesothelioma patients [41].

Chemotherapy

Systemic therapy is the only potential treatment option for the majority of MPM patients. There are few randomized data assessing the role of chemotherapy versus best supportive care (BSC). Sponsored by The British Thoracic Society and Cancer Research UK, a large three arms Phase III trial comparing polichemotherapy (mitomycin 6 mg/m^2 , vinblastine 6 mg/m^2 and cisplatin 50 mg/m² schedule) plus BSC versus vinorelbine plus BSC versus BSC alone started in 2000. This study did not show any significant advantage in terms of OS among the three arms [42]. Although the study was not powered to detect a difference between chemotherapy arms, exploratory analysis suggested that vinorelbine merits further investigation. Moreover, in this trial BSC were compared with the 'old' chemotherapeutic schedules: no data are available about the actual standard treatment (cisplatin/antifolate combination) compared with BSC. O'Brien and coworkers observed how the early versus delayed use of chemotherapy (mitomycin 6 mg/m², vinblastine 6 mg/m² and cisplatin 50 mg/m² schedule) in the management of patients with stable symptoms provided an extended period of symptom control, and a trend to survival advantage [43]. A more recent clinical trial reported that cisplatin and vinorelbine first-line chemotherapy in nonresectable MPM is an active regimen with a RR of 29.6% and a median survival of 16.8 months [44]. Several new cytotoxic agents with definite activity in mesothelioma have recently been evaluated, including gemcitabine and the antifolates raltitrexed and pemetrexed. The cisplatin/gemcitabine combination has showed modest activity with an acceptable toxicity profile in a Phase II clinical trial, as frontline treatment of patients with MPM [45]. Two Phase II studies described the therapeutic effect of carboplatin and gemcitabine in the first-line setting: it resulted as a valid option in the treatment of MPM due to its acceptable toxicity profile and the good RRs (26 and 20%, respectively) [46,47]. The multitargeted antifolate pemetrexed and raltitrexed were shown to have activity in MPM as a single agent and in combination with platinum compounds [11,48,49]. In a multicenter Phase III study involving 448 chemo-naive patients, those treated with pemetrexed plus cisplatin had a longer median OS (12.1 months) than those treated with cisplatin alone (9.3 months) and had an objective RR (shrinkage of the tumor by \geq 50%) of 41 versus 16.7% [11]. Furthermore, the raltitrexed/ cisplatin combination also improved OS compared with cisplatin alone in a population of 250 patients in a randomized Phase III study [49]. The magnitude of the survival benefit was similar in both studies: a 2.8-month increase in median survival in the pemetrexed study (from 9.3 to 12.1 months) and a 2.6 months increase in the raltitrexed study. However, in the pemetrexed trial this difference was statistically significant, while in the other study the survival improvement had borderline significance, probably due to the more limited sample size. With the demonstration of a survival advantage in these two Phase III studies utilizing the combination of cisplatin with an antifolate versus cisplatin alone, other combinations - such as cisplatin/gemcitabine - are not being further studied for patients with untreated advanced MPM. Even though no randomized clinical trials comparing these regimens has been conducted so far, available data suggest that cisplatin with an antifolate should be the reference regimen in patients with MPM. Considering that many MPM patients are unfit to receive a cisplatin-based chemotherapy, a number of schedules used carboplatin, instead of cisplatin, in an attempt to reduce toxicity maintaining the same

survival benefit. In fact, MPM is a disease of the older patient, with a median age of onset of 74 years [50]. The typical nonhematological toxicity profile of cisplatin (gastrointestinal, neurologic and renal) is questionable in the context of a palliative treatment, especially for poor performance and elderly patients. Carboplatin has the potential advantages of having a better adverse effect profile and better ease of administration. The combination of pemetrexed and carboplatin was found to be synergistic in preclinical models and active and well tolerated in a Phase I trial in MPM patients, with a reported RR of 32% [51]. Starting from these data, some combined schedules containing carboplatin, instead of cisplatin, were tested in MPM patients in an attempt to reduce toxicity maintaining the same survival outcomes [52,53]. In a Phase II trial of 102 MPM patients treated with pemetrexed plus carboplatin, a similar TTP (6.5 months) and OS (12.7 months) were observed as in the Phase III trial of pemetrexed/cisplatin [52]. The toxicity profile seemed to be better in the pemetrexed/ carboplatin trial than in the pemetrexed/cisplatin trial, especially considering the nonhematological toxicity. A 76-patient Phase II study reported a TTP of 8.0 months, a median survival of 14 months, and a RR of 25% using the same regimen [53]. Moreover, no significant difference was observed in terms of overall disease control (60.4 vs 66.9%, p=0.47), TTP (7.2 vs 7.5 months, p=0.42) and survival (10.7 vs 13.9 months, p=0.12) between elderly patients compared with younger individuals in a retrospective analysis of pooled data from the two Phase II trials of pemetrexed and carboplatin as first-line therapy [54]. Data from the International Expanded Access Program (EAP) confirmed the activity of pemetrexed plus cisplatin and pemetrexed plus carboplatin in 1704 chemo-naive MPM patients not amenable to curative surgery, demonstrating clinically similar time to progressive disease and 1-year survival rates. In particular, the pemetrexed plus cisplatin group demonstrated a RR of 26.3% compared with 21.7% for the pemetrexed plus carboplatin group, with 1-year survival rates of 63.1 versus 64.0% and median TTP disease of 7 versus 6.9 months [55].

Unfortunately, all MPM patients progress after firstline treatment. Second-line chemotherapy is being increasingly used in the clinical practice, because patients are frequently still healthy at the time of disease progression. Until recently, most MPM chemotherapy trials have focused on chemo-naive patients, with few providing results to guide decisions regarding second line therapy [56]. Therefore, its role in MPM is to be proved yet. A noteworthy activity of pemetrexed, both alone and combined with carboplatin, as secondline treatment following prior platinum-based chemotherapy was reported [57]. In a randomized, multicenter Phase III study examining pemetrexed as second line chemotherapy versus BSC, treatment with pemetrexed provided clinical benefit with a statistically significant improvement in TTP (3.8 vs 1.5 months), whereas improvement in OS was not seen, possibly due to the influence of poststudy therapy on the BSC arm [58]. However, because the cisplatin/pemetrexed regimen has recently become standard in the treatment of first line MPM patients [11], second line chemotherapy should focus on other compounds. Very few prospective trials of second-line chemotherapy in pemetrexed-pretreated MPM patients have been undertaken (Table 4).

Combined modality treatment

Multimodality approaches have been developed in order to reduce local recurrence and systemic spread. Surgery was employed in the form of P/D or EPP in combination with various forms of radiation treatment and chemotherapy [31,59–63]. Surgical resection with intrapleural and systemic chemotherapy showed disappointing results with a high morbidity rate. EPP followed by high-dose external beam RT (54 cGy) achieved a median survival of 33.8 months in stages I and II compared with a median survival of 10 months in stages III and IV, demonstrating the best local control ever achieved in mesothelioma [39]. The Brigham and Women's Hospital in Boston reported that the median survival of 183 patients treated between 1980 and 1997 was 19 months with 2- and 5-year survival rates of 38 and 15%, respectively [64]. This safe approach offered improved survival only for certain subgroups of patients. In particular, patients with epithelial cell type, lack of extra-pleural nodal involvement and negative surgical margins have a median survival approaching 5 years [8]. This and other studies indicate that more effective strategies should be sought to increase local control and better staging procedures should be developed [65].

Another interesting approach is the use of preoperative chemotherapy. In the neo-adjuvant setting, chemotherapy seems to improve the resectability rates and survival without altering the surgery mortality rates [66,67]. The Swiss pilot study administered three cycles of gemcitabine/cisplatin followed by EPP in 19 patients with stages I-III MPM. Induction therapy RR was 32%. EPP was performed in 16 patients without perioperative mortality and 13 patients received postoperative RT. Median survival time was 23 months. The other neoadjuvant Phase II study using gemcitabine/cisplatin was performed at Memorial Sloan-Kettering (NJ, USA), but focused on patients with stage III and IV disease; induction therapy RR was 26%. All patients underwent postoperative external beam radiation therapy (54 cGy). Patients who underwent EPP had a median survival of 33.5 months, while patients who were unable to undergo resection had a median survival of 9.7 months (p = 0.01), suggesting that neoadjuvant chemotherapy is feasible and also helps to select patients who would

Table 4. Second-line therapy in pemetrexed pretreated malignant pleural mesothelioma patients.						
Regimen	Patients (n)	RR (%)	CBR (%)	Medium TTP (months)	Medium OS (months)	Ref.
Re-challenge with pemetrexed-containing chemotherapy						
Pemetrexed/platinum	17	NR	65	NR	NR	[148]
Pemetrexed ± carboplatin	31	19	48	3.8	10.5	[149]
Chemotherapy with other agents						
Oxaliplatin ± gemcitabine	18	22	50	NR	NR	[150]
Vinorelbine + gemcitabine	30	10	43.3	2.8	10.9	[151]
Erlotinib + bevacizumab	24	0	50	2.2	5.8	[152]
Oxaliplatin ± gemcitabine	29	7	45	2.2	5.6	[153]
Weekly vinorelbine	63	16	84	NR	9.6	[154]
NGR-hTNF	57	2	42	2.8	12.1	[135]
Vinorelbine	43	11.6	39.5	2.1	5.3	[155]
Thalidomide	22	6	56	3.6	11	[156]
Sorafenib	31	4	64	3.7	14.6	[157]
Sunitinib	22	27	NR	3.7	8.2	[158]
Belinostat	13	0	15	1	5	[109]
CBR: Clinical benefit rate (partial response + stable disease); NR: Not reported; OS: Overall survival; RR: Response rate TTP: Time to progression.						

benefit most from surgical resection. These results also led to the development of a Swiss trial and a multicenter US trial testing the standard first-line regimen for MPM – pemetrexed/cisplatin – as induction therapy for stage I to III MPM patients before EPP and RT. Krug and colleagues demonstrated the feasibility of this trimodality approach. The toxicities were comparable to those reported in the prior Phase III trial [11] without any impact on surgical and radiation therapy risks. The pathological complete RR was 5% and the radiological RR was 33%. Although this seems slightly less than 41% RR reported in the Phase III trial, response is particularly difficult to assess in this population with earlystage MPM. The median OS was 16.8 and 21.9 months in all enrolled patients and in patients undergoing EPP, respectively. The 2-year survival was 37% and approximately 20% of patients were estimated to survive more than 3 years. This suggested that a subgroup of patients is more likely to benefit from this aggressive approach. An exploratory subgroup analysis indicated that radiological response, but not other factors, were associated with improved survival. Complete or partial response were associated with nearly twice the median survival when compared with stable or progressive disease (26.0 vs 13.9 months) [68]. Hoffmann and colleagues investigated the feasability in stage III MPM patients of the implementation of cold-plasma coagulation on the pleura, pericardium and diaphragm into an established therapeutic algorithm consisting of P/D and hyperthermic intrathoracal chemoperfusion therapy. The underlying rationale was the prevention of cardiotoxic effects during hyperthermic intrathoracal chemoperfusion as well as accidental translocation of malignant cells to the abdomen. Until now the authors observed 1-year relapse-free survival without severe side effects [69].

Nowadays, multimodality treatment is far from perfect and it should be studied further through clinical trials.

Future perspective

Biomarkers

There are no biomarkers in clinical use for MPM. In fact, MPM remains a rare disease and indeed the small number of patients plus the accessibility of a uniform tumor population renders the search for biomarker very difficult. However, biomarkers would be helpful in managing three clinical aspects of MPM: early diagnosis, prognosis, and treatment outcome prediction.

Diagnostic biomarkers

The biomarkers osteopontin, soluble mesothelin-related protein (SMRP), and megakaryocyte potentiating factor (MPF) currently show the most promise for diagnosis, but each has some limitations [70,71]. Osteopontin is a glycoprotein regulated by proteins in cell-signaling pathways that are associated with asbestos-induced carcinogenesis. Mesothelin, a cell-surface glycoprotein that functions in cell-to-cell adhesion, is expressed by normal mesothelial cells and highly overexpressed in MPM as well as in other malignancies such as lung cancers. It is synthesized as a precursor 69-kDa protein and forms membrane-bound mesothelin and a soluble MPF. Abnormal splicing events and enzymatic cleavage from membrane-bound mesothelin lead to the synthesis of a soluble mesothelin, and that the SMRP found in serum include both the soluble mesothelin and the soluble MPF. Osteopontin is a marker of the duration of asbestos exposure, but lacks specificity for mesothelioma, while both SMRP and MPF lack sensitivity for detecting nonepithelial subtypes. In a recent study, serum SMRP, MPF, and osteopontin levels were measured in 66 patients with mesothelioma, 20 healthy control subjects, and 81 others with asbestos-related lung disease, benign pleural effusions, or other cancers. At a specificity of 95%, the sensitivity for detecting mesothelioma was 34% for MPF, 47% for osteopontin, and 73% for SMRP; combining the three biomarkers did not improve sensitivity [72].

Prognostic biomarkers

Elevated SMRP was found to be a significant negative prognostic marker in MPM patients [73]. However, the prognostic impact of SMRP in MPM is not yet conclusive. Recent studies have shown that loss of p16 is associated with poor survival [74.75]. In particular, microarray analysis of 99 specimens of malignant mesotheliomas found homozygous deletion of p16 to be a significant independent adverse prognostic factor in pleural mesotheliomas, with a median survival of 10 months for p16-deleted cases versus 34 months for nondeleted cases (p = 0.001) [74]. This is consistent with a prior study by Borczuk and colleagues that identified loss of p16 immunoreactivity to be an independent predictor of poor survival in peritoneal mesotheliomas [76].

The high microvessel density has been associated with poor survival [77], and proteins involved in regulating angiogenesis have been implicated in the prognosis of MPM. A reduced level of BAX, a tumor suppressor gene downregulated by tumor hypoxia (the engine of angiogenesis), has been associated with a poor outcome [78]. Elevated levels of VEGF in pleural effusion are associated with diminished survival in MPM patients [79], and VEGF overexpression as monitored by IHC independently predicts short survival in MPM patients (p = 0.0002) [80]. High levels of VEGF and FGF2, or co-expression of TGF- β , VEGF, FGF1, and FGF2 are also associated with a poor outcome [81]. PTEN expression was found as a strong predictor of survival in 126 mesothelioma patients [82]. In particular, comparing any PTEN expression versus no expression, median survival time was significantly longer (log rank test p = 0.0001) in patients with PTEN expression (15.5 months; 95% CI: 3.8; 27.2 vs 9.7 months; 95% CI: 7.9; 11.7) and the cox regression analysis revealed an association between PTEN expression and survival (p = 0.003) independently from the histological subtype (p = 0.7). Microarray technology has been used to investigate gene signatures that could be used to predict MPM survival and progression. A four-gene signature comprising KIAA097, GDP-dissociation inhibitor 1, cytosolic thyroid hormone-binding protein and an expressed sequence tag similar to the L6 tumor antigen (which correctly classified a training sample into good and poor prognostic groups [83] predicted the correct outcome in a significant number of cases, supporting the identification of novel disease-specific and treatmentspecific prognostic molecular marker candidates [84]. The presence of an 11-gene, oncogene-driven-pathway signature, correlated with a stem-cell-like expression profile, is associated with a poor prognosis in patients with MPM [85]. In the same way, a large gene-expression analysis identified and validated aurora kinases as predictive of outcome. In fact, mitosis or proliferation, diploidy, and S-phase fraction were identified as significant indices, and increased expression of regulators of mitosis and cell-cycle control were observed in more aggressive cancers [77]. Pass and colleagues investigated whether specific microRNAs could segregate a largely surgically treated group of mesotheliomas into good or bad prognosis categories [86]. A training set of 44 and a test set of 98 mesothelioma tumors were analyzed by a custom microRNA platform, along with nine mesothelioma cell lines and three normal mesothelial lines. Functional implications as well as downstream targets of potential prognostic microRNAs were investigated. Increased expression of hsa-miR-29c* predicted a more favorable prognosis, and overexpression of the microRNA in mesothelioma cell lines resulted in significantly decreased proliferation, migration, invasion, and colony formation. Moreover, major epigenetic regulation of mesothelioma is mediated by hsa-miR-29c* and was shown through downregulation of DNA methyltransferases as well as upregulation of demethylating genes. Nevertheless, the clinical use of biomarkers in MPM is still inconclusive and needs further evaluation.

Predictive biomarkers: pharmacogenomic

There are no established predictive factors that can be used to optimize treatment in MPM.

For targeted therapy, low VEGF serum levels may be useful in predicting the response to treatment with bevacizumab. In fact, in a Phase II randomized trial evaluating the addition of the anti-VEGF monoclonal antibody bevacizumab to gemcitabine plus cisplatin, an higher baseline plasma VEGF levels correlated with shorter progression-free survival (PFS) (p = 0.02) and OS (p = 0.0066) [87].

For chemotherapy, few studies have identified predictors of the responsiveness to pemetrexed and/ or cisplatin/carboplatin treatment in patients with MPM. It is hypothesized that low expression of excision repair cross-complementation group 1 (ERCC1) might predict increased sensitivity to platinum-based chemotherapy; conversely, high levels of ERCC1 may predict a resistance to platinum-based chemotherapy. However, a high-ERCC1 level might also be a positive prognostic variable because it may increase the removal of carcinogenic DNA lesions. Pemetrexed is a multitarget agent that enters the cell via the reduced folate carrier. It is converted to a series of active polyglutamate derivatives by folylpolyglutamate synthetase. These metabolites inhibit three folate-dependent enzymes, thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide-ribonucleotide formyl transferase (GARFT). However, pemetrexed is a weak inhibitor of GARFT, and when TS (its primary target) is inhibited, tetrahydrofolate oxidation stops and there is no longer a need for DHFR activity. Therefore, most studies have focused on pemetrexed effects on TS. TS mRNA expression levels has been inversely correlated with pemetrexed activity in different tumor cells, whereas other studies have suggested a correlation between high levels of TS protein expression and reduced sensitivity to pemetrexed in colon and lung cancer cells [88,89]. Furthermore, TS mRNA and protein expression were predictive of responsiveness in patients with advanced breast cancer treated with pemetrexed alone and in patients with non-small-cell lung cancer treated with pemetrexed/ gemcitabine neoadjuvant therapy, respectively [90]. In a recent retrospective analysis, Righi et al. investigated the correlation between baseline expression levels of TS and ERCC1 genes, which were evaluated by real-time polymerase chain reaction and by immunohistochemistry (using the H-score) in MPM patients treated with pemetrexed-based chemotherapy [91]. They observed that low TS protein levels are predictive of improved TTP (p = 0.02) and OS (p = 0.019) when patients were divided according to the median H-score. Conversely, the researchers did not find a significant correlation between TS mRNA and outcome. Another retrospective analysis of TS and ERCC-1 protein expression by immunohistochemistry in 99 MPM patients treated with the carboplatin/pemetrexed regimen found that TS expression was a predictor of clinical outcome [92]. In particular, the immunohistochemical detection of TS expression was found predictive of clinical outcome. In fact, compared with patients with high TS expression, the patients with low TS expression had a significantly higher probability to achieve disease control to carboplatin/pemetrexed chemotherapy (p=0.027), a significantly longer PFS (p=0.017) and a significantly longer OS (p = 0.022). Moreover, the TS-mRNA analysis confirmed immunohistochemical data. Retrospective studies on candidate predictive biomarkers in MPM specimens may provide strong rationale for future trials. However, the optimization/ standardization of methodologies, as well as the use of large and uniformly treated cohorts and the incorporation of both emerging candidate biomarkers and genotype studies, are critical before prospective trials can identify the best biomarkers for personalized MPM chemotherapy [93]. Probably, considering the rarity of MPM, the creation of a collaborative network which would allow analyzing the role of several biomarkers in a greater number of uniformly treated patients with MPM may be a good strategy.

Assessment of tumor response

Assessment of the response with conventional criteria based on CT scan measurements is challenging, owing to the circumferential and axial pattern of growth of MPM. However, adequate response evaluation is crucial for the identification of active drugs. The modified RECIST criteria have been developed and validated by Byrne and Nowak [94]. Although they are already being used in current clinical trials, they have been criticized based on the high grade of interobserver variability documented in the assessment of tumor response classification in MPM [94-97] and on theoretical studies of mesothelioma growth according to nonspherical models [98]. Furthermore, some morphological characteristics of MPM, such as growth in the axial direction or along the lung fissures, cannot be captured by any of the proposed CT-based response criteria. Therefore, alternative measurement modalities are being developed [99,100]. FDG-PET seems to be useful to assess the response to treatment. In fact, there is growing evidence that therapy-induced changes in tumor FDG uptake might predict response and patient outcome early in the course of treatment. In a study of 22 patients evaluated by FDG-PET and CT imaging at baseline and after two cycles of therapy, eight out of 20 evaluable patients showed a decrease of 25% or more in tumor FDG uptake (as measured by standard uptake value [SUV]) and were defined as having a metabolic response. Metabolic response correlated to PFS, which was 14 months in responders and 7 months in nonresponders. By contrast, no correlation was found between PFS and the radiological response evaluated

by CT imaging. Patients with a metabolic response had a trend towards a longer OS [101]. A total glycolytic volume (TGV) analysis of FDG-PET uptake could represent an interesting development in the assessment of response and prediction of patient outcome in MPM. In 17 MPM patients evaluated after two cycles of first-line chemotherapy with carboplatin and pemetrexed, the metabolic response, defined as any TGV reduction, was significantly correlated to TTP, with a median TTP for metabolic responders of 15.8 versus 5.6 months for nonresponders (p = 0.004). Moreover, patients with a metabolic response had a trend towards longer OS (mean OS 25.4 vs 17.5 months), but this difference did not reach statistical significance (p= 0.20). The sensitivity of this method in comparison to a singlepixel evaluation (SUV_{max}) should be evaluated in larger prospective series [102]. In an other study, 30 patients were suitable for both radiological and ¹⁸F-FDG PET analysis after one cycle of chemotherapy. Cox regression analysis demonstrated a statistically significant relationship between a fall in TGV and improved patient survival (p = 0.015), whereas neither a reduction in the maximum standardized uptake value (p = 0.097) nor CT (p = 0.131) demonstrated a statistically significant association with patient survival [103]. Yoshida and coworkers proposed that Cu-labeled Fab could be useful for ERC/mesothelin-specific PET imaging, thus facilitating improved diagnosis of patients with earlystage mesothelioma [104]. Therefore, metabolic imaging has the potential to improve the care of patients receiving chemotherapy for mesothelioma by the early identification of responding patients. This technology may also be useful in the assessment of new systemic treatments for mesothelioma.

Percentage changes in SMRP levels were recently found as a potentially useful marker of disease course [105]. In fact, in a series of 21 patients receiving systemic therapy, percentage change in SMRP more than 10% correlated with the radiologic assessment by a trained thoracic radiologist (p < 0.001), by formal RECIST (p = 0.008), or by modified RECIST (p < 0.001). Furthermore, all seven patients who underwent surgical resection with negative margins had elevated preoperative SMRP levels that fell to normal postoperatively and rising SMRP was observed in all patients with radiologic disease progression. These findings should be validated prospectively for a role as an objective adjunctive measure of disease course in both clinical trials and clinical practice.

Target therapy

Malignant mesothelioma cells show an increased or dysregulated growth. The knowledge of molecular pathways alterations specific for MPM is basic to discover biomarkers as useful predictive or prognostic tools and to develop and test novel targeted agents [7,13]. Although not entirely comprehensive, the most intriguing molecular pathways for the imminent targeted therapeutic strategies are pointed out as follow. The main ongoing clinical trials are showed in Table 5.

Histone regulation

Epigenetic regulation of tumor suppressor genes through chromatin condensation and decondensation has emerged as an important mechanism that leads to tumorigenesis. A family of histone acetyltransferases and deacetylases (HDACs) regulates this balance, with the latter facilitating chromatin condensation, thus preventing gene transcription, resulting in the loss of heterozygosity of tumor suppressors. Inhibition of this process, coupled with a similar inhibition of nonhistone protein deacetylation, ultimately leads to the promotion of apoptosis, cell cycle arrest, and inhibition of angiogenesis. Preclinical data highlighting the effectiveness of HDAC inhibition in MPM cell lines and mouse xenograft models has led to early phase clinical trials in patients with MPM [106]. Suberoylanilide hydroxamic acid (vorinostat), an oral inhibitor of class I and II HDACs, also represses expression of the *TS* gene, which is the principal target of pemetrexed. There were two objective responses to suberoylanilide hydroxamic acid in the 13 MPM patients enrolled in a Phase I trial [107]. A double-blind, placebo-controlled Phase III trial is

Table 5. Molecular pathways and clinical trials for malignant pleural mesothelioma.				
Study design	Agents	Target		
Setting: I line				
Phase II, III	Bevacizumab + CDDP + pemetrexed vs placebo + CDDP + pemetrexed	VEGF		
Phase II	Bortezomib + CDDP	Ubiquitine proteosome		
Phase II	Vatalanib	PDGFR β , VEGFR1, 2 and 3		
Phase II	Bevacizumab + CDDP + pemetrexed	VEGF		
Phase II	Bevacizumab + CBDCA + pemetrexed	VEGF		
Phase I/II	Cediranib + CDDP + pemetrexed vs placebo + CDDP + pemetrexed	VEGFRs		
Phase I	VS	PDGFR β and KIT		
Setting: I & II line				
Phase II	Placebo + CDDP + pemetrexed	PDGFR β and KIT		
Phase II	Semaxanib	VEGFR2		
Setting: II line				
Phase III	Doxorubicin ± Onconase [®]	NF-κB nuclear translocation		
Phase III	Vorinostat	Class I and II histone deacetylases		
Phase II	Bortezomib	Ubiquitine proteosome		
Phase II	Bortezomib + oxaliplatin	Ubiquitine proteosome		
Phase II	Onconase	NF-κB nuclear translocation		
Phase II	Belinostat	Class I and II histone deacetylases		
Phase II	Everolimus	mTOR		
Phase II	Imatinib + gemcitabine	PDGFR β and KIT		
Phase II	Sunitinib	PDGFR β , VEGFR1, 3, KIT and RET		
Phase II	Vandetanib vs vinorelbine	VEGFR2, 3, RET and EGFR		
Phase II	NGR-hTNF	CD13		
Phase I	SS1P	Mesothelin		
Phase I	MORAb-009	Mesothelin		
Setting: maintainance CT				
Phase II	NGR-hTNF	CD13		
Phase III	Thalidomide	VEGF, FGF and TNF α		

ongoing in which patients are randomized to receive vorinostat 300 mg oral twice daily for three consecutive days of every 7-day period (repeated weekly in a 21-day cycle), plus BSC or placebo plus BSC. The primary end points of the vorinostat trial are OS and tolerability. Patient accrual is underway, recruitment continues after two interim analyses and the results remain blinded [108].

Ramalingam and colleagues conducted a Phase II study with belinostat, a class I and II HDAC inhibitor, in patients with relapsed MPM [109]. Patients received belinostat at 1000 mg/m² intravenously on days 1–5 of a 3-week (21-day) cycle as second-line therapy. The primary end point was RR. No objective responses were observed, thus indicating that belinostat is not active as monotherapy against recurrent MPM.

Preclinical data suggest that the coupling of HDACi therapy to chemotherapy should be more effective [110,111]. A Phase I trial of vorinostat in combination with cisplatin and pemetrexed in advanced solid tumors found an overall RR of 10%, with 58% of patients exhibiting stable disease, including three of five patients (60%) with MPM [112]. In a Phase II trial, valproic acid plus doxorubicin appeared an effective chemotherapic regimen in patients with refractory or recurrent MPM and with a good performance status (Karnofsky 80–100) showing a RR of 16% and a disease control rate of 36% [113].

Cell cycle regulators & apoptosis: NF-κB pathway

Within the NF- κ B pathway, the activated p65 subunit of NF-KB translocates to the nucleus to activate genes that protect the cell from apoptosis (inhibitors of apoptosis). Moreover, activation of the NF-κB pathway can stimulate proliferation and reduce the effectiveness of chemotherapy and ionizing radiation. Therapeutic targeting of TNF- α /NF- κ B signaling (e.g., bortezomib and ranpirnase) decreases drug resistance and increases cytotoxicity in MPM cells [114,115]. However, ranpirnase and bortezomib affect many other targets apart from NFkB pathway: tRNA, rRNA, mRNA as well as the noncoding RNA (microRNAs), proteasome and focal adhesion kinases. Bortezomib is currently being evaluated in three mesothelioma trials, both as a single agent and in combination with cisplatin [201]. The drug ranpirnase has shown promising results: in a Phase II MPM trial, single-agent ranpirnase resulted in a 5% RR, a 43% stable disease rate, and a median OS of 6 months [116]. A Phase III trial compared the efficacy and safety of doxorubicin 60 mg/m² (doxorubicin was one of the most active single agents at the time the study was planned) every 3 weeks with or without ranpirnase 240 µg/m² weekly in cycle one and 480 µg/m² in subsequent cycles (for a maximum of six cycles). A

total of 413 MPM patients were involved, 203 treated with ranpirnase and doxorubicin and 210 treated with doxorubicin alone [117]. The primary end point was OS, and secondary end points included PFS, RR, safety, and disease-related symptoms. There was no significant difference in OS (median survival time: 11.1 versus 10.7 months; hazards ratio 1.02, 95% CI 0.82-1.26) in the intent-to-treat population, but there was a significant advantage in survival in favor of doxorubicin plus ranpirnase in a preplanned analysis that included 130 pretreated patients (median survival time: 10.5 versus 9 months; hazards ratio 1.49, 95% CI 1.02-2.17). The combination of ranpirnase and doxorubicin was safe and feasible in unresectable MPM and showed a significant impact on survival of pretreated patients compared with doxorubicin alone. However, at present doxorubicin does not represent the most active drug in the armamentarium available to the clinicians to treat MPM.

The phosphoinositide 3-kinase/AKT/mTOR pathway

The phosphoinositide 3-kinase-AKT pathway is activated by many growth factors and interacts with mTOR. Activation of mTOR results in phosphorylation of its effectors, the best studied of which are eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and S6 kinase 1 (S6K1). Hyperphosphorylation of 4E-BP1 inhibits 4E-BP binding to eukaryotic initiation factor 4E (eIF4E), activating selective translation of cyclin D1, Bcl-2, Bcl-xL, and VEGF mRNA, among others. Rapamycin, a natural macrolide approved for human use to prevent allograft rejection, is a potent inhibitor of mTOR. Temsirolimus and everolimus are nonimmunosuppressive analogues of rapamycin that show activity in patients with metastatic renal cancer [117,118]. In the clinical setting, a Phase II study of everolimus is ongoing in patients with relapsed MPM [201]. The primary end point of this study is to determine the 4-month PFS in unresectable MPM patients treated with everolimus. The secondary end points are the RR and disease control rate in patients with measurable disease by RECIST and modified RECIST criteria; to determine OS of these patients; and to evaluate the frequency and severity of toxicities associated with this treatment regimen. The patients receive oral everolimus once daily on days 1-28. There is another ongoing Phase II study of everolimus as a second- or third-line therapy for the treatment of advanced MPM. This study, starting from preclinical data that revealed a strong correlation between loss of NF2 and activation of mTORC1 (coherent with sensitivity to the growth-inhibitory effect of rapamycin), will also evaluate NF2 loss as a biomarker for predicting sensitivity to everolimus [201]. In fact, there is loss

of heterozygosity of 22q12 in almost 100% of MPM cases with mutations of the neurofibromatosis type 2 gene (NF2) and of the INK4a/ARF locus (encoding p16 and p14/ARF) [119,120]. The functional inactivation of NF2 leads to tumor development in a 'permissive' (INK4a/ARF deficient) background, thus representing a new potential therapeutic target [121]. Furthermore, NF2-negative MPMs display unregulated mTORC1 signaling and are sensitive to rapamycin, thus providing a preclinical rationale for prospective, biomarker-driven clinical studies of mTORC1 inhibitors in these tumors [122].

The PDGFR pathway

MPM cell lines express PDGFR-β, while normal mesothelial cells express PDGFR-a [123]. Despite promising preclinical data, early studies that tested imatinib mesylate failed to achieve any responses in untreated and pretreated patients in four Phase II trials [124-127]. The poor expression of c-Kit could explain the resistance to imatinib in MPM patients. In vitro experiments demonstrated that imatinib enhances sensitivity of MPM cell lines to chemotherapy, and synergizes selectively with gemcitabine and pemetrexed in PDGFR-β-positive mesothelioma cells [128,129]. In animal models, imatinib mesylate enhances the therapeutic effects of gemcitabine in human malignant mesothelioma xenografts [129]. A Phase II trial has been launched to study imatinib combined with low-dose gemcitabine as a second-line treatment in MPM expressing either PDGFR- β or c-Kit [201]. In this trial, patients receive oral imatinib at a dose of 400 mg/day, together with intravenous gemcitabine at a dose of 500 mg/m² on days 1 and 8 of a 21-day cycle, for a maximum of six cycles. The primary end point of the study is RR. A Phase I trial testing the combination of cisplatin/pemetrexed plus imatinib in a first-line setting is ongoing [201].

The VEGF & VEGFR pathway

There is a strong rationale for inhibition of VEGF signaling in MPM because mesothelioma patients have the highest VEGF levels of any solid tumor patients [130]. Elevated VEGF levels in pleural effusion are associated with diminished survival in MPM patients [77]. Similarly, VEGF overexpression, as detected by IHC, independently predicts short survival in MPM patients (p = 0.0002) [79]. Moreover, VEGF and VEGF-C expression in mesothelioma correlates with microvessel density, and high microvessel density is associated with poor survival [80]. Thus, several antiangiogenic agents that target the vascular VEGF pathway, such as semaxanib (SU5416), vatalanib (PTK787), thalidomide, bevacizumab, sorafenib,

and sunitinib have been evaluated or are still being evaluated for MPM. Phase II studies of semaxanib (SU5416), vatalanib (PTK787), thalidomide, and sorafenib have demonstrated only modest single agent activity that is comparable to other single agents used to treat MPM. The final results of sunitinib, a multitargeted TKI of VEGFR and PDGFR, in a Phase II trial as a second-line therapy in patients with progressive MPM during or after first-line chemotherapy with platinum and an antimetabolite (pemetrexed or gemcitabine) were recently presented [131]. Unfortunately, sunitinib showed only modest activity in previously treated, giving a partial response in five patients (10%) out of 53 patients. The median TTP was 3.4 months and the median OS was 6.7 months. Another trial testing sunitinib as both front-line and salvage therapy settings is ongoing at the National Cancer Institute in Canada [132].

Angiogenic inhibition with the monoclonal antibody bevacizumab provides a survival benefit in colorectal carcinoma and non-small-cell lung cancer. However, a front-line Phase II randomized trial (n = 115) using cisplatin and gemcitabine with or without bevacizumab did not show an improvement in RR or survival with the addition of bevacizumab [87]. A subgroup analysis noted that higher baseline plasma VEGF levels were correlated with shorter progression-free (p = 0.02) and OS (p = 0.0066). This suggests that antiangiogenic therapy could benefit some patients with MPM, and several ongoing MPM studies with bevacizumab may further define which patients should receive antiangiogenic treatment [133,201].

A randomized Phase II trial of vandetanib (a selective inhibitor of VEGFR-2, VEGFR-3, RET and EGFR) versus vinorelbine is still ongoing to evaluate the efficacy and safety in 66 pretreated MPM patients [201]. NGR-hTNF, a novel antiangiogenic drug, is still in development. The antivascular effects of TNF- α provided the rationale for developing a vascular targeting strategy that aimed to increase local antitumor activity and enable systemic administration of therapeutic doses. Towards this end, a recombinant fusion protein of human TNF- α and a NGR peptide that binds specifically to CD13 expressed on the tumor blood vessels of MPM was engineered [134]. In a Phase II trial, NGR-hTNF administered at a low dose (0.8 mg/m² intravenously every 3 weeks) in a second-line setting in MPM patients showed some efficacy in terms of PFS (2.8 months) and OS (12.1 months), with a good toxicity profile [135]. Other antiangiogenic agents in ongoing clinical trials include AZD2171, which targets KDR, Flt-1 and -4, and PDGFR, and pazopanib or GW786034, which targets VEGFR-1, -2, and -3 and PDGFR [201].

Targeting mesothelin

One of the more prominent areas of research in MPM targeted therapies is the use of monoclonal antibodies to mesothelin. Mesothelin is a 40-kDa cell surface protein that is attached to the cell membrane by a glycosylphospatidylinositol anchor. Mesothelin is an attractive candidate for targeted therapy given its limited expression on normal tissues and high cell surface expression in several tumors especially malignant mesothelioma. To target mesothelin, a recombinant immunotoxin, SS1P, was developed consisting of an antimesothelin Fv (SS1) fused to PE38, a 38-kDa portion of Pseudomonas exotoxin A. Hassan and colleagues conducted a Phase I trial of SS1P as a intravenous bolus infusion to patients with mesothelin-expressing MPM, demonstrating that SS1P is well tolerated with an initial evidence of activity in a subgroup of heavily pretreated patients [136]. Recent studies about continuous infusion of antimesothelin recombinant immunotoxin SS1P showed no significant advantage over bolus dosing, and further clinical development of SS1P is proceeding by bolus dosing in combination with chemotherapy [137]. There have been developed a mouse-human chimeric IgG1k monoclonal antibody, MORAb-009, antagonizing human mesothelin. Preclinical data were promising [138] and a Phase I trial enrolling patients with mesothelin-positive expressing cancers has been conducted, demonstrating that MORAb-009 is well tolerated [139]. Phase II studies of MORAb-009 in different mesothelin-expressing cancers are ongoing. A high affinity fully human mesothelin-antibody, M912, has been developed. Preclinical data suggests that M912 specifically lyses mesothelin-positive cells likely by antibody-dependent cellular cytotoxicity (ADCC), without affecting mesothelin-negative cells [140].

The HGF/MET pathway

The c-Met receptor is a tyrosine kinase located on Chr 7q31. It is the only known receptor for HGF/SF, and it mediates all HGF/SF-induced biological activities. Multiple signaling pathways are activated downstream of c-MET, including the Ras/ Erk, phosphoinositide 3-kinase/Akt, and c-Src kinase pathways [141,142]. simian virus 40 infection of human mesothelial cells induces Met receptor activation via an autocrine loop [143]. Moreover, an HGF/SF/c-Met autocrine loop has been demonstrated both in MPM cell lines and in MPM tissue samples, and overexpression of HGF and c-Met has been associated with increased microvessel density as well as with increased matrix metalloproteinase expression [144]. In particular, c-MET is overexpressed in MPM tissues compared with normal pleura, and the expression of the Met protein has been detected by IHC in 74% to 100% of paraffin-embedded mesothelioma tumor specimens but not in normal mesothelial cells. In addition, HGF/ SF expression has been detected by IHC in 40% to 85% of mesothelioma specimens [145]. HGF/SF can also be detected by ELISA in the majority of pleural effusions from patients with mesothelioma [146]. In the preclinical setting, SU11274, a small molecule tyrosine kinase/c-MET inhibitor, induced inhibition of cell growth in some MPM cell lines but not in nonmalignant mesothelial cells [147]. In particular, SU11274 induced inhibition of cell migration, cell motility, and HGF-induced signal transduction. Moreover, cell lines harboring the T1010I mutation (H513, H2596) exhibited a dramatic reduction of cell growth in response to SU11274. Interestingly, the nonresponding MPM cell lines did not show a significant alteration in growth with HGF. There are several strategies for inhibiting c-Met. If additional preclinical tests verify c-Met as an important target in mesothelioma, this receptor may have promise as a target in future clinical trials. At present, several cMET inhibitors are available in clinical setting, even if no specific Met inhibitors have been tested in clinical trials for MPM.

Conclusion

MPM is a rare aggressive neoplasm with a poor prognosis. Locoregional therapies have a limited role in highly selected patients. Systemic therapy is the only option for the majority of patients. Recently the use of platinum compounds combined with an antifolate has become the major clinical option in the first-line setting. Second-line therapies are being increasingly used in MPM patients, although their role and the optimal regimens remain to be defined yet. An improvement in the knowledge of the molecular alterations that are specific for MPM will allow the discovery of useful predictive and prognostic biomarkers and the development of new targeted therapies. However, the development of a more effective management of this rare disease will derive from an integrated multidisciplinary approach involving the medical oncologist, the surgeon, the radiation oncologist and the molecular biologist.

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Executive summary

- Malignant pleural mesothelioma (MPM), the most common primary tumor of the pleura, is an aggressive tumor with a poor prognosis and a median survival of approximately 12 months.
- Approximately 80% of malignant pleural mesothelioma can be attributed to asbestos fiber exposure.
- Correlation between clinical, imaging and pathological findings is critical to a correct and rapid diagnosis.
- The clinical course of these patients varies widely, ranging from slowly progressive to more aggressive disease. Two prognostic scoring systems have been devised according to European Organization for Research and Treatment of Cancer and Cancer and Leukemia Group B.

Treatment

- Pleurectomy/decortication and extrapleural pneumonectomy are the two major types of surgical interventions. Surgery has a limited role and only in highly selected patients.
- Radiotherapy alone has probably no major role in disease control and survival.
- Systemic therapy is the only potential treatment option for the majority of patients.
- Randomized trials have recently confirmed that combining antifolates with platinum compounds confers a survival benefit.
- There is increasing evidence from single-arm trials that second-line chemotherapy is not only feasible but also active. No standard therapy has yet been defined in the second-line setting.
- A trimodality approach with the standard first-line regimen as induction therapy before extrapleural pneumonectomy and RT has been proposed for selected stage I to III MPM patients.
- Adequate response evaluation is a cornerstone for the identification of active treatments.

Future perspective

- An improvement in the knowledge of molecular alterations and key pathways involved in MPM will allow the discovery of biomarkers as useful predictive or prognostic tools and of novel targeted agents.
- Treatments tailored to the biological and genetic characteristics of a patient's tissue will offer better outcomes in the future.
- A multidisciplinary approach and integration of preclinical studies into standard clinical practice is mandatory for improving survival and quality of life for MPM patients.

Bibliography

Papers of special note have been highlighted as:

- of interest
- of considerable interest
- Robinson BW, Lake RA. Advances in malignant mesothelioma. N. Engl. J. Med. 353(15), 1591–1603 (2005).
- 2 Peto J, Decarli A, La Vecchia C, Levi F, Negri E. The European mesothelioma epidemic. *Br. J. Cancer* 79(3–4), 666–672 (1999).
- 3 Carbone M, Kratzke RA, Testa Jr. The pathogenesis of mesothelioma. *Semin. Oncol.* 29(1), 2–17 (2002).
- 4 Zucali PA, De Vincenzo F, Simonelli M, Santoro A. Future developments in the management of malignant pleural mesothelioma. *Expert Rev. Anticancer Ther.* 9(4), 453–467 (2009).
- 5 Curran D, Sahmoud T, Therasse P, Van Meerbeeck J, Postmus PE, Giaccone G. Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. J. Clin. Oncol. 16(1), 145–152 (1998).
- Basis for actual prognosis formulation in clinical practice.

- Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. Chest 113(3), 723–731 (1998).
- Basis for actual prognosis formulation in clinical practice.
- Zucali PA, Ceresoli GL, De Vincenzo F et al. Advances in the biology of malignant pleural mesothelioma. *Cancer Treat. Rev.* DOI: 10.1016/j.ctrv.2011.01.001 (2011) (Epub ahead of print).
- 8 Sugarbaker DJ, Jaklitsch MT, Bueno R et al. Prevention, early detection, and management of complications after 328 consecutive extrapleural pneumonectomies. J. Thorac. Cardiovasc. Surg. 128(1), 138–146 (2004).
- 9 Ahamad A, Stevens CW, Smythe WR et al. Intensity-modulated radiation therapy: a novel approach to the management of malignant pleural mesothelioma. Int. J. Radiat. Oncol. Biol. Phys. 55(3), 768–775 (2003).
- Ceresoli GL, Gridelli C, Santoro A. Multidisciplinary treatment of malignant pleural mesothelioma. *Oncologist* 12(7), 850–863 (2007).

- 11 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. 21(14), 2636–2644 (2003).
- Pivotal trial that led to US FDA approval of pemetrexed for mesothelioma.
- 12 Fennell DA, Gaudino G, O'byrne KJ, Mutti L, Van Meerbeeck J. Advances in the systemic therapy of malignant pleural mesothelioma. *Nat. Clin. Pract. Oncol.* 5(3), 136–147 (2008).
- 13 Zucali PA, Giaccone G. Biology and management of malignant pleural mesothelioma. *Eur. J. Cancer* 42(16), 2706–2714 (2006).
- 14 Belli C, Fennell D, Giovannini M, Gaudino G, Mutti L. Malignant pleural mesothelioma: current treatments and emerging drugs. *Expert Opin. Emerg. Drugs* 14(3), 423–437 (2009).
- 15 Pasello G, Favaretto A. Molecular targets in malignant pleural mesothelioma treatment. *Curr. Drug Targets* 10(12), 1235–1244 (2009).
- 16 Flores RM, Zakowski M, Venkatraman E *et al.* Prognostic factors in the treatment of malignant pleural mesothelioma at a large tertiary referral center. *J. Thorac. Oncol.* 2(10), 957–965 (2007).

Review: Clinical Trial Outcomes Zucali, De Sanctis, De Vincenzo et al.

- 17 Boutin C, Viallat Jr, Van Zandwijk N et al. Activity of intrapleural recombinant γ-interferon in malignant mesothelioma. Cancer 67(8), 2033-2037 (1991).
- Mimura T, Ito A, Sakuma T et al. Novel 18 marker D2-40, combined with calretinin, CEA, and TTF-1: an optimal set of immunodiagnostic markers for pleural mesothelioma. Cancer 109(5), 933-938 (2007).
- Takeda M, Kasai T, Enomoto Y et al. 9p21 19 deletion in the diagnosis of malignant mesothelioma, using fluorescence in situ hybridization analysis. Pathol. Int. 60(5), 395-399 (2010).
- Chiosea S, Krasinskas A, Cagle PT, 20 Mitchell KA, Zander DS, Dacic S. Diagnostic importance of 9p21 homozygous deletion in malignant mesotheliomas. Mod. Pathol. 21(6), 742-747 (2008).
- Hanna A, Pang Y, Bedrossian CW, Dejmek A, 21 Michael CW. Podoplanin is a useful marker for identifying mesothelioma in malignant effusions. Diagn. Cytopathol. 38(4), 264-269 (2010)
- 22 Flores-Staino C, Darai-Ramqvist E, Dobra K, Hjerpe A. Adaptation of a commercial fluorescent in situ hybridization test to the diagnosis of malignant cells in effusions. Lung Cancer 68(1), 39-43 (2010).
- 23 Heelan RT, Rusch VW, Begg CB, Panicek DM, Caravelli JF, Eisen C. Staging of malignant pleural mesothelioma: comparison of CT and MR imaging. AJR Am. J. Roentgenol. 172(4), 1039-1047 (1999)
- Flores RM, Akhurst T, Gonen M, Larson SM, 24 Rusch VW. Positron emission tomography defines metastatic disease but not locoregional disease in patients with malignant pleural mesothelioma. J. Thorac. Cardiovasc. Surg. 126(1), 11–16 (2003).
- 25 Erasmus JJ, Truong MT, Smythe WR et al. Integrated computed tomography-positron emission tomography in patients with potentially resectable malignant pleural mesothelioma: Staging implications. J. Thorac. Cardiovasc. Surg. 129(6), 1364-1370 (2005).
- Truong MT, Marom EM, Erasmus JJ. 26 Preoperative evaluation of patients with malignant pleural mesothelioma: role of integrated CT-PET imaging. J. Thorac. Imaging 21(2), 146-153 (2006).
- Rusch VW. A proposed new international 27 TNM staging system for malignant pleural mesothelioma from the International Mesothelioma Interest Group. Lung Cancer 14(1), 1-12 (1996).

- Basis for actual staging system in ... clinical practice.
- Benamore RE, O'doherty MJ, Entwisle JJ. Use 28 of imaging in the management of malignant pleural mesothelioma. Clin. Radiol. 60(12), 1237-1247 (2005).
- Van Meerbeeck JP, Boyer M. Consensus report: 29 pretreatment minimal staging and treatment of potentially resectable malignant pleural mesothelioma. Lung Cancer 49(Suppl. 1), S123-S127 (2005).
- Flores RM, Pass HI, Seshan VE et al. 30 Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. J. Thorac. Cardiovasc. Surg. 135(3), 620-626 (2008).
- Largest series of surgical patients comparing extrapleural pneumonectomy to pleurectomy decortication.
- Rusch VW, Venkatraman ES. Important 31 prognostic factors in patients with malignant pleural mesothelioma, managed surgically. Ann. Thorac. Surg. 68(5), 1799-1804 (1999).
- 32 Pinton G, Brunelli E, Murer B et al. Estrogen receptor-\beta affects the prognosis of human malignant mesothelioma. Cancer Res. 69(11), 4598-4604 (2009).
- Edwards JG, Abrams KR, Leverment JN, 33 Spyt TJ, Waller DA, O'Byrne KJ. Prognostic factors for malignant mesothelioma in 142 patients: validation of CALGB and EORTC prognostic scoring systems. Thorax 55(9), 731-735 (2000).
- Sugarbaker DJ. Macroscopic complete 34 resection: the goal of primary surgery in multimodality therapy for pleural mesothelioma. J. Thorac. Oncol. 1(2), 175-176 (2006).
- 35 Bolukbas S, Manegold C, Eberlein M, Bergmann T, Fisseler-Eckhoff A, Schirren J. Survival after trimodality therapy for malignant pleural mesothelioma: radical pleurectomy, chemotherapy with cisplatin/pemetrexed and radiotherapy. Lung Cancer 71(1), 75-81 (2011).
- Martini N, Bains MS, Beattie EJ Jr. Indications 36 for pleurectomy in malignant effusion. Cancer 35(3), 734-738 (1975).
- Treasure T, Waller D, Tan C et al. The 37 mesothelioma and radical surgery randomized controlled trial: the Mars feasibility study. J. Thorac. Oncol. 4(10), 1254-1258 (2009).
- Rusch VW, Rosenzweig K, Venkatraman E 38 et al. A Phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J. Thorac. Cardiovasc. Surg. 122(4), 788-795 (2001).

- Ahamad A, Stevens CW, Smythe WR et al. 39 Promising early local control of malignant pleural mesothelioma following postoperative intensity modulated radiotherapy (IMRT) to the chest. Cancer J. 9(6), 476-484 (2003).
- Allen AM, Den R, Wong JS et al. Influence of 40 radiotherapy technique and dose on patterns of failure for mesothelioma patients after extrapleural pneumonectomy. Int. J. Radiat. Oncol. Biol. Phys. 68(5), 1366-1374 (2007).
- Scorsetti M, Bignardi M, Clivio A et al. 41 Volumetric modulation arc radiotherapy compared with static gantry intensitymodulated radiotherapy for malignant pleural mesothelioma tumor: a feasibility study. Int. J. Radiat. Oncol. Biol. Phys. 77(3), 942-949 (2010)
- Muers MF, Stephens RJ, Fisher P et al. Active 42 symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. Lancet 371(9625), 1685-1694 (2008).
- Important Phase III trial which compared active symptom control to chemotherapy with either vinorelbine or mitomycin, vinblastine or cisplatin.
- 43 O'Brien ME, Watkins D, Ryan C et al. A randomised trial in malignant mesothelioma (M) of early (E) versus delayed (D) chemotherapy in symptomatically stable patients: the MED trial. Ann. Oncol. 17(2), 270-275 (2006).
- Sorensen JB, Frank H, Palshof T. Cisplatin 44 and vinorelbine first-line chemotherapy in nonresectable malignant pleural mesothelioma. Br. J. Cancer 99(1), 44-50 (2008).
- 45 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 60(2), 259-263 (2008).
- Favaretto AG, Aversa SM, Paccagnella A et al. 46 Gemcitabine combined with carboplatin in patients with malignant pleural mesothelioma: a multicentric Phase II study. Cancer 97(11), 2791-2797 (2003).
- 47 Aversa SM, Favaretto AG. Carboplatin and gemcitabine chemotherapy for malignant pleural mesothelioma: a Phase II study of the GSTPV. Clin. Lung Cancer 1(1), 73-75 (1999).
- 48 Scagliotti GV, Shin DM, Kindler HL et al. Phase II study of pemetrexed with and without folic acid and vitamin B12 as front-line therapy in malignant pleural mesothelioma. J. Clin. Oncol. 21(8), 1556-1561 (2003).

Treatment of malignant pleural mesothelioma Review: Clinical Trial Outcomes

- Van Meerbeeck JP, Gaafar R, Manegold C 49 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. 23(28), 6881-6889 (2005)
- Hayat MJ, Howlader N, Reichman ME, 50 Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist 12(1), 20-37 (2007).
- Thodtmann R, Depenbrock H, Dumez H 51 et al. Clinical and pharmacokinetic Phase I study of multitargeted antifolate (LY231514) in combination with cisplatin. J. Clin. Oncol. 17(10), 3009-3016 (1999).
- 52 Ceresoli GL, Zucali PA, Favaretto AG et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. J. Clin. Oncol. 24(9), 1443-1448 (2006).
- Defines the potential role of carboplatin/pemetrexed as alternative to cisplatin/pemetrexed.
- Castagneto B, Botta M, Aitini E et al. 53 Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). Ann. Oncol. 19(2), 370-373 (2008).
- Ceresoli GL, Castagneto B, Zucali PA et al. 54 Pemetrexed plus carboplatin in elderly patients with malignant pleural mesothelioma: combined analysis of two Phase II trials. Br. J. Cancer 99(1), 51-56 (2008).
- Santoro A, O'brien ME, Stahel RA et al. 55 Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaive patients with malignant pleural mesothelioma: results of the International Expanded Access Program. J. Thorac. Oncol. 3(7), 756-763 (2008).
- Defines the potential role of carboplatin/pemetrexed as alternative to cisplatin/pemetrexed.
- 56 Ceresoli GL, Zucali PA, Gianoncelli L, Lorenzi E, Santoro A. Second-line treatment for malignant pleural mesothelioma. Cancer Treat. Rev. 36(1), 24-32 (2010).
- Sorensen JB, Sundstrom S, Perell K, 57 Thielsen AK. Pemetrexed as second-line treatment in malignant pleural mesothelioma after platinum-based first-line treatment. J. Thorac. Oncol. 2(2), 147-152 (2007).

- Jassem J, Ramlau R, Santoro A et al. Phase III 58 trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. J. Clin. Oncol. 26(10), 1698-1704 (2008).
- Hilaris BS, Nori D, Kwong E, Kutcher GJ, 59 Martini N. Pleurectomy and intraoperative brachytherapy and postoperative radiation in the treatment of malignant pleural mesothelioma. Int. J. Radiat. Oncol. Biol. Phys. 10(3), 325-331 (1984).
- Rusch V, Saltz L, Venkatraman E et al. A 60 Phase II trial of pleurectomy/decortication followed by intrapleural and systemic chemotherapy for malignant pleural mesothelioma. J. Clin. Oncol. 12(6), 1156-1163 (1994)
- Lee JD, Perez S, Wang HJ, Figlin RA, 61 Holmes EC. Intrapleural chemotherapy for patients with incompletely resected malignant mesothelioma: the UCLA experience. J. Surg. Oncol. 60(4), 262-267 (1995).
- Rice TW, Adelstein DJ, Kirby TJ et al. 62 Aggressive multimodality therapy for malignant pleural mesothelioma. Ann. Thorac. Surg. 58(1), 24-29 (1994).
- Sauter ER, Langer C, Coia LR, Goldberg M, 63 Keller SM. Optimal management of malignant mesothelioma after subtotal pleurectomy: revisiting the role of intrapleural chemotherapy and postoperative radiation. J. Surg. Oncol. 60(2), 100-105 (1995).
- Sugarbaker DJ, Flores RM, Jaklitsch MT et al. 64 Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J. Thorac. Cardiovasc. Surg. 117(1), 54-63 (1999).
- Retrospective study showing prolonged survival for epithelioid, node negative, and margin negative patients.
- Maggi G, Casadio C, Cianci R, Rena O, 65 Ruffini E. Trimodality management of malignant pleural mesothelioma. Eur. J. Cardiothorac. Surg. 19(3), 346-350 (2001).
- Flores RM, Krug LM, Rosenzweig KE et al. 66 Induction chemotherapy, extrapleural pneumonectomy, and postoperative high-dose radiotherapy for locally advanced malignant pleural mesothelioma: a Phase II trial. J. Thorac. Oncol. 1(4), 289-295 (2006).
- Basis for multimodality treatment of malignant pleural mesothelioma.
- Stahel R, Weder W. Neoadjuvant chemotherapy 67 in malignant pleural mesothelioma. Lung Cancer 49, S69-S70 (2005).

- Krug LM, Pass HI, Rusch VW et al. 68 Multicenter Phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. J. Clin. Oncol. 27(18), 3007-3013 (2009).
- Hoffmann M, Bruch HP, Kujath P, Limmer S. 69 Cold-plasma coagulation in the treatment of malignant pleural mesothelioma: results of a combined approach. Interact. Cardiovasc. Thorac. Surg. 10(4), 502-505 (2010).
- Robinson BW, Creaney J, Lake R et al. 70 Mesothelin-family proteins and diagnosis of mesothelioma. Lancet 362(9396), 1612-1616 (2003)
- Pass HI, Lott D, Lonardo F et al. Asbestos 71 exposure, pleural mesothelioma, and serum osteopontin levels. N. Engl. J. Med. 353(15), 1564-1573 (2005).
- Creaney J, Yeoman D, Demelker Y et al. 72 Comparison of osteopontin, megakaryocyte potentiating factor, and mesothelin proteins as markers in the serum of patients with malignant mesothelioma. J. Thorac. Oncol. 3(8), 851-857 (2008).
- 73 Cristaudo A, Foddis R, Vivaldi A et al. Clinical significance of serum mesothelin in patients with mesothelioma and lung cancer. Clin. Cancer Res. 13(17), 5076-5081 (2007).
- 74 Lopez-Rios F, Chuai S, Flores R et al. Global gene expression profiling of pleural mesotheliomas: overexpression of aurora kinases and P16/CDKN2A deletion as prognostic factors and critical evaluation of microarray-based prognostic prediction. Cancer Res. 66(6), 2970-2979 (2006).
- Kobayashi N, Toyooka S, Yanai H et al. 75 Frequent p16 inactivation by homozygous deletion or methylation is associated with a poor prognosis in Japanese patients with pleural mesothelioma. Lung Cancer 62(1), 120-125 (2008).
- 76 Borczuk AC, Taub RN, Hesdorffer M et al. P16 loss and mitotic activity predict poor survival in patients with peritoneal malignant mesothelioma. Clin. Cancer Res. 11(9), 3303-3308 (2005).
- Edwards JG, Swinson DE, Jones JL, 77 Muller S, Waller DA, O'byrne KJ. Tumor necrosis correlates with angiogenesis and is a predictor of poor prognosis in malignant mesothelioma. Chest 124(5), 1916-1923 (2003).
- Kokturk N, Firat P, Akay H et al. Prognostic 78 significance of Bax and Fas ligand in erionite and asbestos induced Turkish malignant pleural mesothelioma. Lung Cancer 50(2), 189-198 (2005).

Review: Clinical Trial Outcomes Zucali, De Sanctis, De Vincenzo et al.

- 79 Strizzi L, Catalano A, Vianale G et al. Vascular endothelial growth factor is an autocrine growth factor in human malignant mesothelioma. J. Pathol. 193(4), 468-475 (2001).
- Demirag F, Unsal E, Yilmaz A, Caglar A. 80 Prognostic significance of vascular endothelial growth factor, tumor necrosis, and mitotic activity index in malignant pleural mesothelioma. Chest 128(5), 3382-3387 (2005).
- Kumar-Singh S, Weyler J, Martin MJ, 81 Vermeulen PB, Van Marck E. Angiogenic cytokines in mesothelioma: a study of VEGF, FGF-1 and -2, and TGF β expression. J. Pathol. 189(1), 72-78 (1999).
- 82 Opitz I, Soltermann A, Abaecherli M et al. PTEN expression is a strong predictor of survival in mesothelioma patients. Eur. J. Cardiothorac. Surg. 33(3), 502-506 (2008).
- Gordon GJ, Jensen RV, Hsiao LL et al. 83 Using gene expression ratios to predict outcome among patients with mesothelioma. J. Natl Cancer Inst. 95(8), 598-605 (2003).
- 84 Gordon GJ, Rockwell GN, Godfrey PA et al. Validation of genomics-based prognostic tests in malignant pleural mesothelioma. Clin. Cancer Res. 11(12), 4406-4414 (2005).
- Glinsky GV, Berezovska O, Glinskii AB. 85 Microarray analysis identifies a death-fromcancer signature predicting therapy failure in patients with multiple types of cancer. J. Clin. Invest. 115(6), 1503-1521 (2005).
- 86 Pass HI, Goparaju C, Ivanov S et al. hsa-miR-29c* is linked to the prognosis of malignant pleural mesothelioma. Cancer Res. 70(5), 1916-1924 (2010).
- Karrison T, Kindler HL, Gandara DR et al. 87 Final analysis of a multicenter, double-blind, placebo-controlled, randomized Phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients (pts) with malignant mesothelioma. J. Clin. Oncol. 25, 7526 (2007).
- 88 Sigmond J, Backus HH, Wouters D, Temmink OH, Jansen G, Peters GJ. Induction of resistance to the multitargeted antifolate Pemetrexed (ALIMTA) in WiDr human colon cancer cells is associated with thymidylate synthase overexpression. Biochem. Pharmacol. 66(3), 431-438 (2003).
- Ceppi P, Volante M, Ferrero A et al. 89 Thymidylate synthase expression in gastroenteropancreatic and pulmonary neuroendocrine tumors. Clin. Cancer Res. 14(4), 1059–1064 (2008).

- Bepler G, Sommers KE, Cantor A et al. 90 Clinical efficacy and predictive molecular markers of neoadjuvant gemcitabine and pemetrexed in resectable non-small cell lung cancer. J. Thorac. Oncol. 3(10), 1112-1118 (2008)
- 91 Righi L, Papotti MG, Ceppi P et al. Thymidylate synthase but not excision repair cross-complementation group 1 tumor expression predicts outcome in patients with malignant pleural mesothelioma treated with pemetrexed-based chemotherapy. J. Clin. Oncol. 28(9), 1534-1539 (2010).
- Zucali PA, Giovannetti E, Destro A et al. 92 Thymidylate synthase and excision repair cross-complementing group-1 as predictors of responsiveness in mesothelioma patients treated with pemetrexed/carboplatin. Clin. Cancer Res. 17(8), 2581-2590 (2011).
- Zucali PA, Giovannetti E, Assaraf YG, 93 Ceresoli GL, Peters GJ, Santoro A. New tricks for old biomarkers: thymidylate synthase expression as a predictor of pemetrexed activity in malignant mesothelioma. Ann. Oncol. 21(7), 1560-1561 (2010).
- 94 Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann. Oncol. 15(2), 257–260 (2004).
- Basis for actual assessment of response in clinical practice.
- Armato SG 3rd, Oxnard GR, Macmahon H 95 et al. Measurement of mesothelioma on thoracic CT scans: a comparison of manual and computer-assisted techniques. Med. Phys. 31(5), 1105-1115 (2004).
- Armato SG 3rd, Oxnard GR, 96 Kocherginsky M, Vogelzang NJ, Kindler HL, Macmahon H. Evaluation of semiautomated measurements of mesothelioma tumor thickness on CT scans. Acad. Radiol. 12(10), 1301-1309 (2005).
- Armato SG 3rd, Ogarek JL, Starkey A et al. 97 Variability in mesothelioma tumor response classification. AJR Am. J. Roentgenol. 186(4), 1000-1006 (2006).
- Oxnard GR, Armato SG 3rd, Kindler HL. 98 Modeling of mesothelioma growth demonstrates weaknesses of current response criteria. Lung Cancer 52(2), 141-148 (2006).
- Pass HI, Temeck BK, Kranda K, 99 Steinberg SM, Feuerstein IR. Preoperative tumor volume is associated with outcome in malignant pleural mesothelioma. J. Thorac. Cardiovasc. Surg. 115(2), 310-317 (1998).
- 100 Atri M. New technologies and directed agents for applications of cancer imaging. J. Clin. Oncol. 24(20), 3299-3308 (2006).

101 Ceresoli GL, Chiti A, Zucali PA et al. Early response evaluation in malignant pleural mesothelioma by positron emission tomography with [18F] fluorodeoxyglucose. J. Clin. Oncol. 24(28), 4587-4593 (2006).

New techniques to evaluate response to treatment.

- 102 Ceresoli GL, Chiti A, Gianoncelli L et al. Early response evaluation in MPM by total glycolitic volume analysis of serial FDG-PET scans. Presented at: The IX International Conference of the IMIG. Amsterdam, The Netherlands, 25-27 September 2008.
- 103 Francis RJ, Byrne MJ, Van Der Schaaf AA et al. Early prediction of response to chemotherapy and survival in malignant pleural mesothelioma using a novel semiautomated 3-dimensional volume-based analysis of serial ¹⁸F-FDG PET scans. J. Nucl. Med. 48(9), 1449-1458 (2007).
- 104 Yoshida C, Sogawa C, Tsuji AB et al. Development of positron emission tomography imaging by 64Cu-labeled Fab for detecting ERC/mesothelin in a mesothelioma mouse model. Nucl. Med. Commun. 31(5), 380-388 (2010)
- 105 Wheatley-Price P, Yang B, Patsios D et al. Soluble mesothelin-related peptide and osteopontin as markers of response in malignant mesothelioma. J. Clin. Oncol. 28(20), 3316-3322 (2010).
- 106 Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat. Rev. Drug Discov. 5(9), 769–784 (2006).
- 107 Krug LM, Curley T, Schwartz L et al. Potential role of histone deacetylase inhibitors in mesothelioma: clinical experience with suberoylanilide hydroxamic acid. Clin. Lung Cancer 7(4), 257-261 (2006).
- 108 Krug LM, Marangolo M, Kindler HL et al. A Phase III, randomized, double-blind, placebo-controlled trial of vorinostat in patients with advanced malignant pleural mesothelioma (MPM) previously treated with systemic chemotherapy. Presented at: The IX International Conference of the IMIG. Amsterdam, The Netherlands, 25-27 September 2008.
- Ramalingam SS, Belani CP, Ruel C et al. 109 Phase II study of belinostat (PXD101), a histone deacetylase inhibitor, for second line therapy of advanced malignant pleural mesothelioma. I. Thorac. Oncol. 4(1), 97-101 (2009).
- 110 Vandermeers F, Hubert P, Delvenne P et al. Valproate, in combination with pemetrexed and cisplatin, provides additional efficacy to the treatment of malignant mesothelioma. Clin. Cancer Res. 15(8), 2818-2828 (2009).

Treatment of malignant pleural mesothelioma Review: Clinical Trial Outcomes

- 111 Marchion D, Munster P. Development of histone deacetylase inhibitors for cancer treatment. Expert Rev. Anticancer Ther. 7(4), 583-598 (2007).
- 112 Chen L, Vogelzang NJ, Blumenschein G et al. Phase I trial of vorinostat (V) in combination with pemetrexed (Pem) and cisplatin (CDDP) in patients with advanced cancer. J. Clin. Oncol. 25, 18088 (2007).
- 113 Scherpereel A, Berghmans T, Lafitte JJ et al. Valproate-doxorubicin: promising therapy for progressing mesothelioma. A Phase II study. Eur. Respir. J. 37(1), 129-135 (2010).
- 114 Gordon GJ, Mani M, Mukhopadhyay L et al. Expression patterns of inhibitor of apoptosis proteins in malignant pleural mesothelioma. J. Pathol. 211(4), 447-454 (2007).
- 115 Adams J, Palombella VJ, Sausville EA et al. Proteasome inhibitors: a novel class of potent and effective antitumor agents. Cancer Res. 59(11), 2615–2622 (1999).
- 116 Mikulski SM, Costanzi JJ, Vogelzang NJ et al. Phase II trial of a single weekly intravenous dose of ranpirnase in patients with unresectable malignant mesothelioma. I. Clin. Oncol. 20(1), 274-281 (2002).
- 117 Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N. Engl. J. Med. 356(22), 2271-2281 (2007).
- 118 Motzer RJ, Escudier B, Oudard S et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled Phase III trial. Lancet 372(9637), 449-456 (2008).
- 119 Cheng JQ, Lee WC, Klein MA, Cheng GZ, Jhanwar SC, Testa JR. Frequent mutations of NF2 and allelic loss from chromosome band 22q12 in malignant mesothelioma: evidence for a two-hit mechanism of NF2 inactivation. Genes Chromosomes Cancer 24(3), 238-242 (1999).
- 120 Jongsma J, Van Montfort E, Vooijs M et al. A conditional mouse model for malignant mesothelioma. Cancer Cell 13(3), 261-271 (2008).
- 121 Thurneysen C, Opitz I, Kurtz S, Weder W, Stahel RA, Felley-Bosco E. Functional inactivation of NF2/merlin in human mesothelioma. Lung Cancer 64(2), 140-147 (2009).
- 122 Lopez-Lago MA, Okada T, Murillo MM, Socci N, Giancotti FG. Loss of the tumor suppressor gene NF2, encoding merlin, constitutively activates integrin-dependent mTORC1 signaling. Mol. Cell Biol. 29(15), 4235-4249 (2009).

- 123 Langerak AW, Van Der Linden-Van Beurden CA, Versnel MA. Regulation of differential expression of platelet-derived growth factor α - and β -receptor mRNA in normal and malignant human mesothelial cell lines Biochim. Biophys. Acta 1305(1-2), 63-70 (1996)
- 124 Mathy A, Baas P, Dalesio O, Van Zandwijk N. Limited efficacy of imatinib mesylate in malignant mesothelioma. a Phase II trial. Lung Cancer 50(1), 83-86 (2005).
- 125 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. 59(1), 149-150 (2007).
- 126 Millward M, Parnis F, Byrne M et al. Phase II trial of imatinib mesylate in patients with advanced pleural mesothelioma. J. Clin. Oncol. 22, 228S (2003).
- 127 Villano JL, Husain AN, Stadler WM et al. A Phase II trial of imatinib mesylate in patients (pts) with malignant mesothelioma (MM). I. Clin. Oncol. 22, 7200 (2004).
- 128 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 62(8), 690-695 (2007).
- 129 Bertino P, Piccardi F, Porta C et al. Imatinib mesylate enhances therapeutic effects of gemcitabine in human malignant mesothelioma xenografts. Clin. Cancer Res. 14(2), 541-548 (2008).
- 130 Linder C, Linder S, Munck-Wikland E, Strander H. Independent expression of serum vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in patients with carcinoma and sarcoma. Anticancer Res. 18(3B), 2063-2068 (1998).
- 131 Nowak AK, Millward M, Francis RJ et al. Final results of a Phase II study of sunitinib as second-line therapy in malignant pleural mesothelioma (MPM). J. Clin. Oncol. 28, 15S (2010).
- 132 Buckstein R, Meyer RM, Seymour L et al. Phase II testing of sunitinib: the National Cancer Institute of Canada Clinical Trials Group IND Program Trials IND.182-185. Curr. Oncol. 14(4), 154-161 (2007).
- 133 Ceresoli GL, Zucali PA, De Vincenzo F et al. Phase II study of the combination of bevacizumab plus pemetrexed and carboplatin as first-line therapy in patients with malignant pleural mesothelioma. Presented at: The IX International conference of the IMIG. Amsterdam, The Netherlands, 25-27 September 2008.

- 134 Curnis F, Sacchi A, Borgna L, Magni F, Gasparri A, Corti A. Enhancement of tumor necrosis factor α antitumor immunotherapeutic properties by targeted delivery to aminopeptidase N (CD13). Nat. Biotechnol. 18(11), 1185-1190 (2000).
- 135 Gregorc V, Zucali PA, Santoro A et al. Phase II study of asparagine-glycine-argininehuman tumor necrosis factor α , a selective vascular targeting agent, in previously treated patients with malignant pleural mesothelioma. I. Clin. Oncol. 28(15), 2604-2611 (2010).
- 136 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 mesothelinexpressing mesothelioma, ovarian, and pancreatic cancers. Clin. Cancer Res. 13(17), 5144-5149 (2007).
- 137 Kreitman RJ, Hassan R, Fitzgerald DJ, Pastan I. Phase I trial of continuous infusion anti-mesothelin recombinant immunotoxin SS1P. Clin. Cancer Res. 15(16), 5274-5279 (2009)
- 138 Hassan R, Ebel W, Routhier EL et al. Preclinical evaluation of MORAb-009, a chimeric antibody targeting tumor-associated mesothelin. Cancer Immun. 7, 20 (2007).
- Hassan R, Cohen SJ, Phillips M et al. Phase I 139 clinical trial of the chimeric anti-mesothelin monoclonal antibody MORAb-009 in patients with mesothelin-expressing cancers. Clin. Cancer Res. 16(24), 6132-6138 (2010).
- 140 Feng Y, Xiao X, Zhu Z et al. A novel human monoclonal antibody that binds with high affinity to mesothelin-expressing cells and kills them by antibody-dependent cellmediated cytotoxicity. Mol. Cancer Ther. 8(5), 1113-1118 (2009).
- 141 Mazzone M, Comoglio PM. The Met pathway: master switch and drug target in cancer progression. FASEB J. 20(10), 1611-1621 (2006).
- 142 Giaccone G, Zucali PA. Src as a potential therapeutic target in non-small-cell lung cancer. Ann. Oncol. 19(7), 1219-1223 (2008).
- 143 Cacciotti P, Libener R, Betta P et al. SV40 replication in human mesothelial cells induces HGF/Met receptor activation: a model for viral-related carcinogenesis of human malignant mesothelioma. Proc. Natl Acad. Sci. USA 98(21), 12032–12037 (2001).
- 144 Tolnay E, Kuhnen C, Wiethege T, Konig JE, Voss B, Muller KM. Hepatocyte growth factor/scatter factor and its receptor c-Met are overexpressed and associated with an increased microvessel density in malignant pleural mesothelioma. J. Cancer Res. Clin. Oncol. 124(6), 291-296 (1998).

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- 145 Klominek J, Baskin B, Liu Z, Hauzenberger D. Hepatocyte growth factor/scatter factor stimulates chemotaxis and growth of malignant mesothelioma cells through c-met receptor. *Int. J. Cancer* 76(2), 240–249 (1998).
- 146 Thirkettle I, Harvey P, Hasleton PS, Ball RY, Warn RM. Immunoreactivity for cadherins, HGF/SF, met, and erbB-2 in pleural malignant mesotheliomas. *Histopathology* 36(6), 522–528 (2000).
- 147 Jagadeeswaran R, Ma PC, Seiwert TY *et al.* Functional analysis of c-Met/hepatocyte growth factor pathway in malignant pleural mesothelioma. *Cancer Res.* 66(1), 352–361 (2006).
- 148 Serke M, Bauer T. Pemetrexed in second-line therapy in patients with malignant pleural mesotelioma. J. Clin. Oncol. 25, 18198 (2007).
- 149 Ceresoli GL, Zucali PA, De Vincenzo F *et al.* Retreatment with pemetrexed-based chemotherapy in patients with malignant pleural mesothelioma. *Lung Cancer* 72(1), 73–77 (2010).

- 150 Serke M, Xanthopoulos A, Bauer T. Second line chemotherapy in malignant pleural mesothelioma with oxaliplatin/gemcitabine. *Ann. Oncol.* 17, 231a (2006).
- 151 Zucali PA, Ceresoli GL, Garassino I *et al.* Gemcitabine and vinorelbine in pemetrexedpretreated patients with malignant pleural mesothelioma. *Cancer* 112(7), 1555–1561 (2008).
- 152 Jackman DM, Kindler HL, Yeap BY et al. Erlotinib plus bevacizumab in previously treated patients with malignant pleural mesothelioma. *Cancer* 113(4), 808–814 (2008).
- 153 Xanthopoulos A, Bauer TT, Blum TG, Kollmeier J, Schonfeld N, Serke M. Gemcitabine combined with oxaliplatin in pretreated patients with malignant pleural mesothelioma: an observational study. *J. Occup. Med. Toxicol.* 3, 34 (2008).
- 154 Stebbing J, Powles T, Mcpherson K *et al.* The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer* 63(1), 94–97 (2009).
- 155 Zucali PA, Lorenzi E, Ceresoli GL *et al.* Vinorelbine (V) in pemetrexed-pretreated

patients (pts) with malignant pleural mesothelioma (MPM). Presented at: *The X International Conference of the IMIG*. Kyoto, Japan 30 August–3 September 2010.

- 156 Pavlakis N, Abraham R, Harvie R. Thalidomide alone or in combination with Cisplatin/Gemcitabine in malignant pleural mesothelioma(MM): interim results of two parallel nonrandomised Phase II studies. *Lung Cancer* 41, S11 (2003).
- 157 Janne PA, Wang XF, Krug LM, Hodgson L, Vokes EE, Kindler HL. Sorafenib in malignant mesothelioma (MM): A Phase II trial of the Cancer and Leukemia Group B (CALGB 30307). J. Clin. Oncol. 25, 7707 (2007).
- 158 Nowak AK, Millward MJ, Francis R, Van Der chaaf A, Musk AW, Byrne MJ. Phase II study of sunitinib as second-line therapy in malignant pleural mesothelioma (MPM). J. Clin. Oncol. 26, 8063 (2008).

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201 ClinicalTrials.gov www.clinicaltrials.gov

