



## Emerging therapies in malignant pleural mesothelioma

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### ABSTRACT

Malignant pleural mesothelioma (MPM) is a rare cancer of the pleural surfaces frequently related to asbestos exposure. It is characterized by a poor prognosis even for patients treated with trimodality therapy, including surgery, chemotherapy and radiotherapy. Moreover, the majority of patients are not candidates for surgery due to disease advanced stage or medical comorbidities. For these patients, the survival rate is even lower and few therapeutic options are currently available. Nevertheless, many interesting novel approaches are under investigation, among which immunotherapy represents one of the most promising emerging strategies. In this review, we will discuss the role of new therapeutic options, particularly immunotherapy, and present the results of the most important and promising clinical trials.

### 1. Introduction

Malignant pleural mesothelioma (MPM) is a rare cancer of the pleura. Its most frequent cause is asbestos exposure, being responsible for about 80% of diagnosis (Carbone et al., 2012). The majority of patients with MPM, with the exception of those with resectable disease and eligible to multimodality therapy, have a poor prognosis, with a medium survival ranging from 12 to 18 months after diagnosis (Wu and de Perrot, 2017). Moreover, survival is usually worse for male patients compared to women (Mancuso and Neal, 2017).

Worldwide MPM incidence is probably underestimated but is unequivocally rising in both developed and developing countries, and will likely peak around 2025 (Patel and Dowell, 2016).

Pleural primary site, poor ECOG performance status, high serum levels of platelets and LDH, advanced age and non-epithelial histology are independent negative prognostic and predictive factors (Herndon et al., 1998; Curran et al., 1998).

Symptoms, typically dyspnea, cough and chest pain, usually occur in a late-stage disease. Typical radiology signs of MPM are pleural thickening, nodules and effusion. Patients history of asbestos exposure is mandatory to collect. Diagnosis needs to be confirmed with pleural biopsy or cytological specimen (Mancuso and Neal, 2017; Curran et al., 1998).

Therapeutic options for MPM include surgery, radiotherapy (RT)

and chemotherapy (CT), which may be combined in a multimodality treatment.

Of note, only 20% of MPM patients are eligible for radical surgery to remove macroscopic disease (R0 or R1 resection) with a 5-years survival rate less than 15%. For patients not suitable for radical surgery, systemic CT represents the treatment backbone (Vogelzang et al., 2003; Cinausero et al., 2018).

Despite the revolutionary advancements seen in the last decade in the treatment of many tumor types, the MPM prognosis has remained substantially the same. Novel targets and treatments are under investigation and strongly needed to improve patients' outcome and raise the bar in MPM treatment.

#### 1.1. Pathobiology

The main cause of MPM is occupational or para-occupational asbestos exposure and the disease generally occurs after a long latency period ranging from 20 to 70 years. As a matter of fact, the incidence is increasing despite the ban on asbestos use in most countries since the 1980s. Moreover, asbestos is still being used in some developing countries. Minerals such as erionite have also been implicated in the development of MPM. Other causes of mesothelioma include irradiation of chest wall or mediastinum and simian virus 40 (Carbone et al., 2012).

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However, about 20% of patients who develop MPM do not have any history of previous exposure to asbestos or to any other known risk factor, suggesting that genetic predisposition may also be involved in MPM pathogenesis (Patel and Dowell, 2016).

In recent years, a better understanding of mesothelioma pathobiology has led to an improved knowledge of its genetics and epigenetics as well as tumor microenvironment and immunobiology.

p53 and p16/p14 genes are frequently inactivated in MPM, leading to inactivation of tumor-suppressing pathways (Yap et al., 2017; Sekido, 2008).

Nasu et al have identified somatic mutations in the BRCA-associated protein 1 (BAP1) suppressor gene in 57–63% of cases. Moreover, germline mutations of this gene predispose to the development of MPM and various other malignancies (Patel and Dowell, 2016; Nasu et al., 2015). Additionally, genomic analysis of mesothelioma has also revealed other mutations, gene fusions or splicing alterations involved in MPM pathogenesis (Woodard et al., 2017; Bueno et al., 2016). The genetic mutation of the neurofibromatosis type 2 (NF2) suppressor gene has been identified in up to 40% of MPM cases. This gene encodes a protein named Merlin, which is one of the crucial elements of the Hippo pathway regulating the invasiveness, proliferation and survival of MPM cells (Sekido, 2008).

Inactivation of large tumor suppressor homolog 2 (LATS2) and 1 (LATS1) has also been found in MPM. Furthermore, the overexpression of focal adhesion kinase (FAK) and the presence of subpopulations of cancer stem cells conferring resistance to chemotherapy (CT) has been identified in preclinical models (Woodard et al., 2017). Targeting such pathways remains a crucial area of active research. Further details on mesothelioma pathobiology will be discussed in treatment-addressed sections of this review.

## 1.2. Treatment of resectable malignant pleural mesothelioma

### 1.2.1. Surgery

Univocal consensus regarding the role of surgery in MPM has not yet been reached. Both extrapleural pneumonectomy (EPP) and lung sparing procedures such as pleurectomy/decortication (P/D) failed in demonstrating a clear survival advantage in phase III clinical trials. Moreover, both procedures are associated with not negligible morbidity and mortality and clinical trials comparing EPP with P/D are lacking. Better outcomes are guaranteed in high-volume centers with adequate expertise (Maziak et al., 2005). To date, no clear prognostic factors have been identified to predict which patients will rapidly recover and benefit from surgery. However, Cao et al identified non-epithelial histology and N2 nodal involvement as predictive factors of poor outcome after EPP, suggesting that patients with similar characteristics should not be directed to this type of surgery (Cao et al., 2011).

A retrospective review of 663 U.S. patients who underwent surgery, showed a worse overall survival (OS) and a greater mortality with EPP compared to P/D (Flores et al., 2008). Moreover, a recent systematic review of the literature conducted by Cao et al suggests lower morbidity (62% vs 28%,  $p < 0.0001$ ) and mortality (6.8% vs 2.9%,  $p = 0.02$ ) and similar survival benefit (13–29 months vs 12–22 months) with P/D compared to EPP (Cao et al., 2014).

### 1.2.2. Multimodality treatment

Radiotherapy plays a key role in palliative setting, local prophylactic irradiation of surgical port sites and in radical treatment. The introduction of intensity modulated RT (IMRT) over the last decade improved efficacy with less toxicity (Mancuso and Neal, 2017). This approach was initially evaluated after EPP (Rusch et al., 2001) and then expanded to preoperative setting (Cho et al., 2014) and to IMRT approach after P/D (Rimmer et al., 2016). The SMART trial showed that neoadjuvant IMRT followed by EPP seems to be safe and feasible, particularly in patients with epithelioid tumors (Cho et al., 2014).

Radical surgery with neoadjuvant RT can achieve a local control of

the disease, but distant metastases will develop in most patients. Thus, the efficacy of induction CT regimen, followed by surgery and subsequent RT have been evaluated in several non-randomized studies and a median OS ranging from 14 to 25.5 months was found for this approach (Patel and Dowell, 2016; Krug et al., 2009). However, we should take into account the high patients selection in these trials (Krug et al., 2009).

In the trimodality therapy setting non-EPP surgeries have demonstrated better outcomes, in terms of both quality of life and survival (Treasure et al., 2011). Carefully selected patients may benefit from multimodality approach but adequately powered randomized trials are required in order to establish the optimal strategy for the integration of CT and RT with surgery.

### 1.3. Treatment of unresectable malignant pleural mesothelioma

CT represents the standard treatment for unresectable MPM in patients with ECOG performance status 0–2 (Cinausero et al., 2018).

Single-agent CT has achieved modest results with a response rate up to 20% (Mancuso and Neal, 2017; Tsao et al., 2009). Compared to best supportive care (BSC), both single agent vinorelbine and cisplatin, vinblastine and mitomycin regimen failed to demonstrate a statistically significant survival benefit (Muers et al., 2008).

The phase III EMPHACIS trial by Vogelzang et al led to the FDA approval of first-line cisplatin plus pemetrexed chemotherapy, demonstrating a significant survival advantage for this regimen compared to single agent cisplatin, with a median OS of 12.1 months compared to 9.7 months in the control arm (Vogelzang et al., 2003). The addition of folic acid and vitamin B12 to CT further improved the outcome while reducing toxicities.

A similar trial compared cisplatin 80 mg/mq plus the antimetabolite raltitrexed to cisplatin alone (van Meerbeeck et al., 2005), showing an improvement of both OS and PFS, comparable to the pemetrexed study. Taking into consideration economic aspects, toxicity profiles and clinical experience, the usually recommended first line regimen is represented by cisplatin plus pemetrexed. Carboplatin plus pemetrexed is a reasonable alternative to prevent toxicities in frail patients, even though the evidence of its efficacy is based on phase II studies (Castagneto et al., 2008; Ceresoli et al., 2006; Katirtzoglou et al., 2010; Ceresoli et al., 2008; Santoro et al., 2008).

Cisplatin plus gemcitabine regimen has been evaluated in phase II trials and represents a valid alternative when pemetrexed is contraindicated (Mancuso and Neal, 2017; Kalmadi et al., 2008). Also carboplatin with gemcitabine has shown a 26% response rate with a good tolerance (Favaretto et al., 2003). To our knowledge, no randomized clinical trial has compared cisplatin plus pemetrexed to cisplatin plus gemcitabine. Conversely, the combination of cisplatin and anthracyclines showed no advantage compared with standard regimens in phase II trials (Ardizzoni et al., 1991; Berghmans et al., 2005).

A phase II trial evaluated the activity of carboplatin-pemetrexed plus bevacizumab as first-line therapy on 77 MPM patients. The primary endpoint (improvement of median PFS from 6 to 9 month compared to standard CT) was not reached (Ceresoli et al., 2013).

However, the multicenter randomized phase III MAPS trial comparing cisplatin-pemetrexed to cisplatin-pemetrexed plus bevacizumab (Zalcman et al., 2016), showed a benefit of about 2 months in both PFS and OS, despite an increased toxicity (grade 3 hypertension, thrombotic events, proteinuria). Based on these results, this triplet represents an option in selected patients.

Notably, according to MED trial first-line CT should be started at diagnosis, even in asymptomatic patients, without a detrimental effect of immediate treatment (O'Brien et al., 2006).

Few data are available about second line therapy. Manegold et al conducted a retrospective analysis to identify potential predictors of survival in MPM patients receiving second-line CT in the setting of EMPHACIS trial (Manegold et al., 2005). The authors reported a longer

survival in patients who received post-study CT (42% of patients) compared with those not receiving second-line therapy. However, some factors (good performance status, early stage, epithelial histology, younger age) characterizing patients treated with second-line CT could have influenced the outcome.

Single agent pemetrexed showed PFS improvement compared to BSC (3.6 vs 1.5 months) in pemetrexed-naïve patients. (Jassem et al., 2008).

Moreover, phase II trials demonstrated improved response rates for gemcitabine, vinorelbine or anthracyclines compared to BSC (Zucali et al., 2012; Skubitz, 2002; Stebbing et al., 2009; Toyokawa et al., 2014). Cisplatin-gemcitabine (Vogelzang, 1999), irinotecan-cisplatin-mitomycin (Fennell et al., 2007), and oxaliplatin-raltitrexed (Fizazi et al., 2003; Porta et al., 2005), have also been investigated as second-line treatment, but prospective trials are lacking.

The role of pemetrexed as maintenance treatment is under investigation (Anon., 2019a).

Moreover, rechallenge with pemetrexed plus platinum-based CT could be considered in patients who have obtained a clinical benefit from first-line CT, as suggested by the clinical trial conducted by Ceresoli et al (Ceresoli et al., 2011).

To date, the American Society of Clinical Oncology guidelines and European Society of Medical Oncology guidelines recommend vinorelbine as second-line therapy particularly in patients for whom clinical trials are not an option.

## 2. New frontiers in the treatment of MPM patients

Several approaches have been studied or are currently under evaluation in an effort to improve systemic treatment for MPM and to identify predictive biomarkers (McCambridge et al., 2018).

### 2.1. Antiangiogenic therapy

Angiogenesis represents a key-factor for tumor growth and progression. In addition to the positive results of bevacizumab in the MAPS trial (Zalcman et al., 2016), several anti-angiogenic small molecules have been investigated.

A randomized phase III trial evaluated thalidomide as maintenance therapy after first-line platinum plus pemetrexed-based CT; however, no improvement in TTP was reported in patients receiving thalidomide compared with those in the BSC arm (Buikhuisen et al., 2013).

Conversely, Grosso et al reported the results of a phase II trial evaluating the combination of cisplatin-pemetrexed plus nintedanib versus cisplatin-pemetrexed alone (Grosso et al., 2017). The authors showed a trend towards improved OS and a statistically significant longer PFS in patients receiving nintedanib (HR 0.54; 95% CI 0.33-0.87).

Unfortunately, the results of the phase III part of LUME-Meso trial did not meet its primary (PFS) and key secondary endpoints. Thus, the use of first-line nintedanib in combination with cisplatin-pemetrexed for patients with epithelioid MPM is not currently supported (Scagliotti et al., 2019).

In two phase II trials, the tyrosine kinase inhibitor (TKI) cediranib as second-line treatment demonstrated an ORR of approximately 10% (Campbell et al., 2012; Garland et al., 2011). Moreover, a phase I study was performed to evaluate the addition of cediranib to standard first-line CT followed by cediranib as maintenance therapy; a median PFS and OS of 13 and 16 months, respectively, was reported (Tsao et al., 2017). The phase II study SWOG S0905, whose results were presented at the 2018 ASCO meeting, confirmed the potential role of cediranib in the same setting: PFS was significantly prolonged in the cediranib arm, compared to placebo (HR 0.69,  $p = 0.096$ , median PFS 7.2 vs 5.6 months) (Anne and Tsao, 2018).

The TKIs sunitinib and vatalanib demonstrated negligible response rates in phase II studies (Laurie et al., 2011; Jahan et al., 2012).

Sorafenib showed a response rate of 6% in MPM chemo naïve or pre-treated patients (Dubey et al., 2010); moreover, another phase II trial showed a response rate of 36% in platinum-based CT pretreated patients (Papa et al., 2013).

In preclinical models, the combination of sorafenib and everolimus has proven to be effective against mammalian target of rapamycin (mTOR) and ERM pathways in tumor cells, suggesting targeted combination therapy as a promising approach against MPM (Pignochino et al., 2015). Preclinical data also showed promising results with the combination of pemetrexed with the c-MET and tubulin inhibitor tivantinib in MPM cell lines; the authors demonstrated synergistic activity between the two agents resulting in inhibition of tumor growth and cell migration (Leon et al., 2014). NCT02049060 is ongoing to evaluate the combination of tivantinib plus carboplatin and pemetrexed (Anon., 2019b).

Moreover, a randomized, placebo-controlled, phase III trial evaluated the experimental antiangiogenic agent NGR-hTNF addition to a standard single agent second line therapy. Notwithstanding preliminary results showed a median PFS of 3.4 vs 1.9 months (Gregorc et al., 2018a), but the primary endpoint OS did not differ between the two treatment cohorts (HR 0.94, 95% C.I. 0.75–1.18;  $p = 0.58$ ) (Gregorc et al., 2018b).

### 2.2. Anti-mesothelin therapeutic strategies

Mesothelin is highly expressed in mesothelioma cancer cells (95% of epithelioid MPM). Thus, the immune-targeting of mesothelin through immunotoxins, antibodies, vaccines and chimeric-antigen receptor T-cells is under evaluation in several phase I/II trials and could be an effective strategy (Katzman and Sterman, 2018; Kiesgen et al., 2018).

The monoclonal antibody amatuximab has been evaluated in different phase I trials showing no response rate (Fujisaka et al., 2015; Hassan et al., 2010). In a phase II study, the combination of this agent with standard first-line CT showed response rate or stable disease rate of 90%, and median OS of 14.8 months, despite no improvement in PFS (Hassan et al., 2014). A double-blind, randomized, phase II trial evaluating the addition of amatuximab to CT has completed recruitment (Anon., 2019c). Antibody-drug conjugates targeting mesothelin have also been investigated in mesothelioma patients. Anetumab ravtansine consists of a human anti-mesothelin antibody conjugated to the maytansinoid tubulin inhibitor DM4. Blumenschein et al conducted a phase I trial demonstrating a durable 75% disease control rate in MPM patients treated with this agent (Blumenschein et al., 2016). Furthermore, NCT02639091 phase I trial is ongoing to evaluate the combination of anetumab ravtansine with cisplatin-pemetrexed in mesothelin-expressing solid tumors (Anon., 2019d).

Another anti-mesothelin antibody conjugated to cytotoxic drug is represented by BMS-986148, currently under investigation in NCT02341625 trial (Anon., 2019e).

A phase I trial assessing the mesothelin targeted immunotoxin LMB-100 in MPM patients is ongoing (Anon., 2019f). Other agents targeting mesothelin have showed preliminary efficacy against mesothelioma in clinical trials, such as recombinant immunotoxins SS1P and RG7787 (McCambridge et al., 2018; Dozier et al., 2017).

### 2.3. EGFR inhibition and microRNA technology

The expression of epidermal growth factor receptor (EGFR) in mesothelioma cancer cells is reported to range from 32 to 97% (Mancuso and Neal, 2017). However, few data are available regarding the inhibition of EGFR through small molecules or monoclonal antibodies in MPM patients. Erlotinib failed to demonstrate activity in a phase II study on 63 mesothelioma patients, with 75% overexpressing EGFR (Garland et al., 2007). Similarly, single-agent gefitinib did not achieve valid response rates (Govindan et al., 2005). Recently, the clinical trial NCT00996567, evaluating the first-line combination of cetuximab plus

platinum-pemetrexed, has completed recruitment (Anon., 2019g).

MicroRNA (miRNA) mimics are small, double-stranded RNA innovative molecules designed to mimic endogenous RNA molecules and useful for gene targeting and silencing approaches. The expression of the miR-15 and miR-16 family miRNAs has been shown to be reduced in MPM tumor specimens, leading to uncontrolled tumor growth. Conversely, the use of miRNA mimics restoring miR-15/16 expression demonstrated to inhibit tumor growth in MPM cell lines (Reid et al., 2013).

Van Zandwijk et al conducted a first-in-human, open-label, phase I study to investigate the safety profile, dosing, and activity of minicells loaded with miR-16-based mimic miRNA, delivering cargos of miR-16 to EGFR-expressing cells (TargomiRs) (Van Zandwijk et al., 2017). The trial showed an acceptable safety profile and signs of activity, further studies are awaited.

#### 2.4. PDGFR inhibition

Mesothelioma cancer cells express both PDGF and PDGFR- $\alpha$ / $\beta$  (Mancuso and Neal, 2017). Thus, several TKIs targeting PDGFR pathway have been studied. Imatinib, currently approved for the treatment of myeloid leukemia and gastrointestinal stromal tumors, demonstrated activity in preclinical models through the induction of apoptosis. However, negative results have been observed in phase I and phase II trials, and none of the mesothelioma patients receiving different doses of single-agent imatinib had a response (Mancuso and Neal, 2017; Mathy et al., 2005).

Notably, preclinical studies showed synergistic effect between imatinib and CT. Tsao et al conducted a phase I trial to evaluate the combination of imatinib and cisplatin-pemetrexed regimen, showing clinical benefit in some patients but poor tolerance to the treatment (Tsao et al., 2014). Another phase I trial showed antitumor activity and manageable toxicity with imatinib plus gemcitabine in the setting of refractory solid tumors; 1 MPM patient out of 5 had a partial response (Ali et al., 2007). The phase II NCT02303899 trial, evaluating the combination of imatinib and gemcitabine in pretreated patients has currently terminated the enrollment (Anon., 2019h).

The TKI dasatinib failed in demonstrating activity in a phase II trial on pretreated MPM patients (Dudek et al., 2012). However, preclinical studies suggest that this agent can modulate sensitivity of cancer cells to pemetrexed through the down-regulation of thymidylate synthase (Monica et al., 2016).

#### 2.5. Inhibition of PI3K/AKT/mTOR signaling

The cellular pathway involving phosphatidylinositol-4,5-bisphosphate 3-kinases (PI3K), mTOR and AKT is crucial in promoting tumor proliferation, growth, differentiation, and tumor motility. Its alterations have been identified also in mesothelioma cancer cells, leading to the hypothesis that targeting this pathway could provide clinical benefit in MPM patients (Mancuso and Neal, 2017).

Monotherapy with the mTOR inhibitor everolimus showed limited activity in a phase II trial, with an ORR of 0–10% (S-HI et al., 2015).

As previously mentioned, preclinical models suggested that the combination of sorafenib and everolimus could be effective in MPM cancer cells (Pignochino et al., 2015).

In preclinical models, the PI3K-mTOR dual inhibitor LY3023414 have demonstrated to have antitumor activity against skin squamous cell carcinoma (Zou et al., 2017), esophageal adenocarcinoma (Zaidi et al., 2017) and colorectal cancer with APC and PI3K mutations (Foley et al., 2017). The first-in-human phase I NCT01655225 trial is currently recruiting to study this agent (Anon., 2019i).

The small molecule apitolisib is a mTOR-PI3K inhibitor which showed modest but durable antitumor activity in the first-in-human phase I study on 120 patients with solid tumors, including 33 MPM patients (Dolly et al., 2016).

Furthermore, inhibition of PI3K and MET pathways has demonstrated to be effective in reducing cell proliferation, motility and survival in in-vitro studies (Kanteti et al., 2016).

#### 2.6. Histone deacetylase inhibitors

The identification of BAP1 mutations in MPM has led to investigate the role of histone deacetylase inhibitors in mesothelioma patients.

The phase III trial on 661 pretreated patients randomly assigned to vorinostat or placebo did not demonstrate a clinically meaningful benefit. Indeed, the authors reported a not clinically significant increase in PFS with vorinostat compared with placebo (6.3 vs 6.1 weeks, HR 0.75, 95%CI 0.63–0.88) with a not statistically significant difference in OS (30.7 vs 27.1 weeks, HR 0.98, 95%CI 0.83–1.17) (Krug et al., 2015). Similarly, belinostat failed to demonstrate benefit in a phase II trial on recurrent MPM (Ramalingam et al., 2009). In a phase II study, presented at ASCO 2018 meeting, tazemetostat showed promising activity in patients with relapsed or refractory MPM with BAP1 loss of function. 31 pts (51%) achieved disease control at 12 weeks and 15 patients (25%) sustained disease control at 24 weeks. No patients discontinued treatment due to adverse events (Zauderer et al., 2018).

#### 2.7. FAK inhibition

The loss of expression of the gene suppressor NF2 has been identified in 40–50% of mesothelioma samples. This gene encodes for a protein (Merlin) that inhibits FAK, an intracellular molecule involved in the intracellular adhesion. Consequently, loss of NF2 leads to altered migration and invasiveness of tumor cells (Mancuso and Neal, 2017).

The small molecule Defactinib is a FAK inhibitor which has demonstrated antitumor activity as maintenance therapy after platinum-pemetrexed CT in preclinical models (Pachter et al., 2015). A phase I study conducted in 9 Asian patients with solid tumors demonstrated good tolerance of defactinib and a durable stable disease of 24 weeks in 2 out of 9 patients (1 with MPM) (Shimizu et al., 2016). The multinational randomized phase II COMMAND trial failed to demonstrate the effectiveness of maintenance therapy with defactinib compared to placebo in MPM patients not progressed on first-line standard CT. Indeed, no benefit on patients' outcome was shown in an interim analysis and the trial stopped enrollment early (McCambridge et al., 2018; Dean Anthony Fennell PB et al., 2014).

A phase I-II trial is currently recruiting to evaluate the combination of Defactinib with Pembrolizumab in various neoplasms, including mesothelioma (Anon., 2019j).

Another FAK inhibitor, GSK2256098, showed an acceptable safety profile and clinical activity in MPM patients, particularly those with loss of Merlin (PFS 23.4 weeks, n = 14) compared with Merlin positive patients (11.4 weeks, n = 9) (Soria et al., 2016).

#### 2.8. Other targeted therapeutic approaches

The Hippo pathway plays a critical role in cell proliferation and survival, and has proven to be dysregulated in MPM through alterations of Hippo genes such as NF2, LATS2, LATS1, and MST1 (Woodard et al., 2017). In 70% of MPM cases, this dysregulation leads to a constitutively activation of the transcription factor Yes-associated protein (YAP), which then promotes proliferative signaling (Woodard et al., 2017; Felley-Bosco and Stahel, 2014). Verteporfin, a photosensitizer agent used in the treatment of neovascular macular degeneration, was found to significantly downregulate transcription in MPM tissue, leading to YAP reduction and suggesting the potential role of YAP as a therapeutic target in mesothelioma (Zhang et al., 2017).

HSP90 inhibitors, such as ganetespib, are also under investigation combined with first-line standard CT in MPM patients (Anon., 2019k).

O'Brien et al performed a single arm phase II trial to evaluate a first-line combination of cisplatin plus bortezomib, a proteasome inhibitor

used in multiple myeloma patients. However, the authors showed a PFS rate at 18 weeks of 53%, which did not meet the criteria for activity to predict success in a phase III trial (O'Brien et al., 2013).

Additionally, it was demonstrated that 60% of MPM patients do not express argininosuccinate synthetase 1 (ASS1), resulting in arginine depletion. Szlosarek et al conducted a phase 2 randomized clinical trial evaluating the addition of pegylated arginine deaminase (Adi-PEG20) to BSC in mesothelioma ASS1 negative patients. They reported an improvement of the primary endpoint PFS in the Adi-PEG20 group compared with patients receiving only BSC (mPFS 3.2 vs 2 months, HR 0.56,  $p = 0.03$ ). Moreover, a phase 1 trial showed a response rate of 78% in MPM patients receiving cisplatin-pemetrexed plus Adi-PEG20 (McCambridge et al., 2018). NCT02709512 trial is currently recruiting mesothelioma patients to evaluate this triplet in tumors with low levels of ASS1 (Anon., 2019).

### 2.9. Immunotherapeutic strategies: from immune checkpoint inhibition to adoptive cell therapy

The relationship between immune system and cancer cells is well known. The immunoeediting represents a dynamic process through which immunosurveillance can induce changes in immunogenicity of tumor cells, leading to the onset of immune-resistant variants (Dozier et al., 2017).

Furthermore, the tumor microenvironment characterizing MPM plays a crucial role and it is characterized by the presence of immunosuppressive elements such as cytokines IL-6 and IL-8, regulatory T-cells (Tregs) and M2 polarized-tumor associated macrophages (Judge et al., 2016; Ujiie et al., 2015). Notably, a worse outcome has been shown to be related with high CD63+ tumor-associated macrophages and low CD8+ tumor infiltrating lymphocytes; conversely, tumors with low CD163+ associated macrophages and high CD20+ lymphocytes had better prognosis (Yamada et al., 2010; Anraku et al., 2008).

One of the main mechanism of immunosurveillance escape is represented by the upregulation of cancer cell surface inhibitory ligands; as such, several clinical trials have been conducted or are currently ongoing to determine the role of checkpoint inhibitors in mesothelioma patients, mainly based on the positive results of these agents in a variety of solid tumors. Indeed, through their ability to block the inhibitory signaling, checkpoint blockers may prevent the downregulation of immune system.

Programmed death-1 (PD-1) is a key immune checkpoint receptor expressed on the surface of activated lymphocytes and natural killer cells. Its binding with the programmed death ligand-1 and 2 (PD-L1 and PD-L2) on cancer and stromal cells, leads to immune cells exhaustion and tumor proliferation (Dozier et al., 2017). PD-L1 is expressed in about 16–40% of MPM, with a higher frequency in sarcomatoid subtype. Furthermore, PD-L1 positivity has been shown to be associated with worse prognosis and to play a crucial role in determining the efficacy of anti-PD-1 novel agents (Cedr s et al., 2015).

The phase Ib KEYNOTE-028 trial reported a 40% clinical benefit rate with manageable toxicity in PD-L1 positive MPM patients receiving monotherapy with the anti-PD-1 monoclonal antibody pembrolizumab (Alley et al., 2017a). A phase II clinical trial described a clinically significant single-agent activity in previously treated patients unselected for PDL-1, reporting a 19% RR and a 66% disease control rate. Moreover, the authors described higher RR and prolonged PFS with increasing PD-L1 expression (Desai et al., 2018).

The anti-PD-1 Nivolumab has also been investigated in second or subsequent lines of therapy. A phase II study reported a disease control rate at 12 weeks of 50%, meeting its primary endpoint (Quispel-Janssen et al., 2019). Goto and colleagues presented at 2017 World Conference of Lung Cancer (WCLC) the preliminary results of the MERIT trial, a phase II multicenter, open-label, single arm study. The ORR achieved in the Nivolumab arm was 29.4%, the median PFS was 6.1 months (95% IC:2.9-NR) and the median OS was not reached yet (Goto et al., 2017).

Nivolumab confirmed to be effective and safe, as single agent therapy, in a real life setting and in MM patients with an ECOG performance status  $\geq 2$  (Hamad et al., 2018).

Avelumab, a monoclonal antibody directed against PD-L1, has being investigated in the phase Ib JAVELIN study; an ORR of 14.3% and 8% in PD-L1 positive and PD-L1 negative MPM patients, respectively, has been reported (Hassan et al., 2016).

Other immune checkpoint inhibitors, such as the cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor Tremelimumab, were studied in clinical trials. CTLA-4 is a glycoprotein expressed by activated T lymphocytes and Tregs, which induces an immune inhibitory signaling through its binding to the ligand B7 (Dozier et al., 2017). A phase II study by Calabr  et al showed a durable partial response rate of 7% in pretreated MPM patients receiving Tremelimumab 15 mg/kg every 3 months, though the primary endpoint was not met (Calabr  et al., 2013). Another phase II trial assessed the role of an intensive schedule of tremelimumab (10 mg/kg every 28 days for 6 cycles, followed by maintenance with tremelimumab every 3 months) showing a control rate of 52% and partial response in 4 out of 29 patients (Calabr  et al., 2015). However, the results of a large phase II DETERMINE trial reported no survival benefit from tremelimumab compared with placebo in the intention-to-treat population (7.7 vs 7.3 months, HR 0.92,  $p = 0.41$ ) (Maio et al., 2017).

The combination of CTLA-4 inhibitors with PD-1/PD-L1 inhibitors is currently under investigation, in order to improve efficacy of mesothelioma systemic treatment. Preliminary results of a randomized phase II trial evaluating Nivolumab, with or without Ipilimumab, in pretreated MPM patients have been presented at the 2017 ESMO annual meeting. The authors showed an ORR of 27.8% in the combination-therapy group, compared with 18.5% in patients receiving only Nivolumab. Disease control rates at 12 weeks was 50% and 44.4%, respectively. Median PFS was 5.6 months for the combination arm and 4 months in the Nivolumab arm, median OS was not reached and 13.6 months, respectively (Zalcman et al., 2017).

Similar results were reported by Disselhorst at the 2017 WCLC with a disease control rate at 12 weeks of 28% for the Nivolumab plus Ipilimumab combination (Disselhorst et al., 2017).

The combination of an anti CTLA-4 antibody, Tremelimumab, with an anti PDL-1 antibody, Durvalumab, was evaluated in a second line setting in the NIBIT-MESO 1 study. The authors found a 28% ORR and 65% disease control rate according to ir-RECIST. The median response duration was 16.1 months. No correlation between baseline PD-L1 and outcome measures was found (Calabr  et al., 2018).

Moreover, the integration of immunotherapy with CT and RT may potentially improve outcome in these patients. Indeed, some studies have suggested that hypofractionated high-dose RT may have an immunomodulatory synergistic effect through the upregulation of TILs and CD8 T lymphocytes (Wu and de Perrot, 2017; Alley et al., 2017b).

Also chemotherapy seems to have an immunostimulatory effect; as a matter of fact, metastatic breast cancer patients receiving taxanes were found to have an increase of immune-related cytokines and immune cells (Wu and de Perrot, 2017). The combination of immunotherapy and CT has shown promising results in preclinical trials on mesothelioma cells (Wu et al., 2014). In the phase II DREAM study, the addition of Durvalumab to standard first-line CT improved 6 months-PFS and ORR, with a good tolerability profile (Nowak et al., 2018).

Immunotherapeutic vaccination and oncolytic virotherapy are also under investigation (Dozier et al., 2017; Anon., 2019m). The adoptive cell therapy, by the utilization of genetically-modified T cell receptor (TCR) and chimeric antigen receptor modified T cell (CAR T cell), represents another novel developing therapeutic strategy (Katzman and Serman, 2018; Dozier et al., 2017).

Several clinical trials are currently ongoing to assess the efficacy of immunotherapeutic strategies and are shown in Table 1.

**Table 1**  
Significant ongoing trials on immunotherapy in MPM patients (as of June 2019; “not yet recruiting” trials excluded).

Treatment strategy	Biological target	Experimental drug	Study number, status, phase
<i>Immunotherapy alone</i>	PD-1	Pembrolizumab	NCT02707666, recruiting, phase 1
			NCT02784171, recruiting, phase 2
			NCT02959463, recruiting, phase 1
			NCT02399371, active not recruiting, phase 2
			NCT02991482, active not recruiting, phase 3
	PD-L1 CTLA-4 PD-1 plus CTLA-4	Nivolumab	NCT03126630, recruiting, phase 1/2
			NCT03063450, recruiting, phase 3
			NCT02497508, completed, phase 2
			NCT01772004, active not recruiting, phase 1
			NCT01843374, active not recruiting, phase 2
PD-L1 plus CTLA-4	Durvalumab plus tremelimumab	NCT02716272, active not recruiting, phase 2	
		NCT02899299, active not recruiting, phase 3	
		NCT03048474, active not recruiting, phase 2	
		NCT02592551, recruiting, phase 2	
		NCT02588131, recruitment status unknown, phase 2	
<i>Immunotherapy plus chemotherapy</i>	CD26 PD-L1 plus chemotherapy PD-L1 plus chemotherapy and radiotherapy. PD-L1 plus VEGF and chemotherapy	YS110 Durvalumab Atezolizumab Atezolizumab plus bevacizumab plus chemotherapy	NCT03762018, recruiting, phase 3
			NCT02141347, completed, phase 1
			NCT03177668, active not recruiting, phase 1/2
			NCT02899195, active not recruiting, phase 2
			NCT03228537, recruiting, phase 1
<i>Anti-mesothelin</i>	Mesothelin targeted immunotoxin	LMB-100 LMB-100 plus SEL-110 LMB-100 followed by pembrolizumab SS1P	NCT02798536, active not recruiting, phase 1
			NCT03436732, completed, phase 1
			NCT03644550, recruiting, phase 2
			NCT01362790, completed, phase 1/2
			NCT00006981, completed, phase 1
<i>Vaccines</i>	Wilms tumor gene (WT-1) Dendritic cells (DC) Oncolytic virus	SS1P plus chemotherapy WT-1 analog peptide vaccine WT1-targeted dendritic cell vaccinations DC vaccine plus chemokine modulatory regimen DC immunotherapy plus MesoPher GL-ONC1	NCT01445392, terminated, phase 1
			NCT01265433, completed, phase 2
			NCT01890980, active not recruiting, phase 2
			NCT02649829, recruiting, phase 1/2
			NCT02151448, completed, phase 1/2
<i>Adoptive cell therapy</i>	TCR CAR T cell	TCR targeting WT-1 CAR T cell targeting mesothelin	NCT03610360, recruiting, phase 2/3
			NCT02714374, active not recruiting, phase 1b
			NCT01766739, active not recruiting, phase 1
			NCT02408016, active not recruiting, phase 1/2
			NCT02414269, recruiting, phase 1
			NCT03907852, recruiting, phase 1/2
			NCT03054298, recruiting, phase 1
			NCT02580747, recruitment status unknown, phase 1
			NCT03638206, recruiting, phase 1/2
			NCT01583686, terminated, phase 1/2
			NCT01355965, completed, phase 1

### 3. Conclusions

The management of MPM still represents a critical challenge. The combination of platinum compounds plus pemetrexed, with or without bevacizumab, is currently the standard first-line CT for MPM patients. Despite the systemic treatment, the prognosis of these patients remains poor, with median OS of approximately 12 months (Mancuso and Neal, 2017). Many therapeutic strategies have been studied or are under development in order to improve the outcome of MPM patients, focusing on the underlying biology and molecular pathways of the disease. Immunotherapy is one of the most promising new therapeutic strategies, with several trials ongoing or already completed. Given the results of the above-mentioned studies by Alley and Zalcman (Alley et al., 2017a; Zalcman et al., 2017), the last version of NCCN guidelines has incorporated Pembrolizumab and Nivolumab with or without Ipilimumab as a treatment option for MPM patients after progression on first-line CT. Based on a subset analysis of these trials, PDL-1 expression seems to be a useful biomarker in identifying patients more likely to benefit from immunotherapeutic strategies. However, these results should be interpreted cautiously, due to the small sample size of the

studies.

When considering data from immunotherapy clinical trials, whether positive or negative, it should not be underestimated the limited mutation rate and the consequent low formation of antigens characterizing mesothelioma tumors (Wu and de Perrot, 2017). This aspect, together with the immunosuppressive pattern of MPM microenvironment, may partially explain the poor efficacy of some novel therapeutic agents.

Additionally, the blockade of immune checkpoints may lead to the upregulation of alternative inhibitory checkpoints, which may result in an adaptive resistance to PD-1 and PD-L1 inhibitors (Dozier et al., 2017). Regarding immunotoxin-based immunotherapy and oncolytic virotherapy, the development of patient-derived antibodies able to neutralize the toxin or the virus could decrease the therapeutic effects.

The current lack of validated biomarkers capable to identify the patients more likely to derive benefit from immunotherapy or other treatment strategies, represents a further critical challenge. Similarly, no biomarker predicting the safety of such drugs and the probability of immune-related toxicity has been identified yet.

A thorough knowledge of mesothelioma biology and micro-environment will be determinant to overcome the mechanisms of

resistance and to develop tailored effective treatments.

Despite the many promising results, to date patients' participation in clinical trials should be encouraged whenever possible.

### Author contributions

All authors actively contributed to draft the manuscript. The last author was involved in revising the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript.

### Declaration of Competing Interest

No conflict of interest nor funding is to be declared for the hand-writing of this manuscript.

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