Bongiovanni *et al. J Cancer Metastasis Treat* 2022;8:44
DOI: 10.20517/2394-4722.2022.78

Journal of Cancer Metastasis and Treatment

Review

Open Access

Immunotherapy in malignant pleural mesothelioma: a long story ended in success

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How to cite this article: Bongiovanni A, Frassoldati A, Calabrò L. Immunotherapy in malignant pleural mesothelioma: a long story ended in success. *J Cancer Metastasis Treat* 2022;8:44. https://dx.doi.org/10.20517/2394-4722.2022.78

Received: 30 Jun 2022 **First Decision:** 1 Aug 2022 **Revised:** 13 Aug 2022 **Accepted:** 23 Sep 2022 **Published:** 8 Oct 2022

Academic Editor: Robert Arthur Kratzke **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Malignant pleural mesothelioma (MPM) is an aggressive and rare disease, mainly due to asbestos exposure, characterized by a poor prognosis. For almost two decades, platinum-based chemotherapy has been the only approved therapeutic regimen for first-line MPM, with an overall survival of 12 months. In the last years, the therapeutic scenario of different tumor types, including MPM, has dramatically changed due to immune checkpoint inhibition. The promising results of this approach have promoted new efforts into clinical research, and many trials investigating novel therapeutic combinations are currently ongoing. The aim of the present review is to provide a comprehensive overview of the most promising immunotherapeutic-based strategies currently under investigation for advanced MPM.

Keywords: Malignant pleural mesothelioma, immunotherapy, immune checkpoint inhibitors, cancer vaccine

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive disease that affects the pleural membranes lining the lungs, characterized by a poor prognosis. Although it is considered a relatively rare tumor, its global rate increased massively over the last four decades due to asbestos exposure, and its continued slow increase

indicates that it has become an epidemic[1]. According to histology, MPM is distinguished into three groups: epithelioid, sarcomatoid, and biphasic type[2,3]. Due to its rapid growth, MPM is generally diagnosed at an advanced stage; consequently, only few patients are suitable for the radical surgical approach (pleuro-pneumonectomy or radical pleural decortication), usually associated with neoadjuvant chemotherapy and adjuvant radiation therapy. Front-line systemic treatment with platinum compounds combined with pemetrexed has been the treatment choice for the majority of MPM patients for almost two decades[4,5]. However, the antitumor efficacy of this regimen is unsatisfactory, with the median overall survival (mOS) of approximately 12 months. Over the last decade, research showed that the angiogenesis process seems to have a key role in MPM progression, which led to the investigation of several antiangiogenetic agents in prospective clinical trials. However, with the exception of the MAPS trial, in which bevacizumab combined with a platinum-based regimen showed a significant improvement in survival compared with chemotherapy alone despite the cardiovascular side effects reported[6], the trials, including the randomized, phase III LUME-Meso-study with nintedanib combined with chemotherapy, failed to demonstrate a survival benefit[7]. Furthermore, the outcome results of second-line regimens approved for relapsed MPM patients were not satisfactory; gemcitabine, vinorelbine, or pemetrexed rechallenge was often utilized in this setting of disease for fit MPM patients, but without a significant improvement in mOS[8].

In the last years, targeting checkpoint inhibitors has dramatically redesigned the therapeutic landscape of different tumor types, and promising results in unresectable MPM subjects, particularly combination regimens, have been recently reported. Consistently, ipilimumab, an anti-cytotoxic T lymphocyte antigen (CTLA)-4 monoclonal antibody (mAb), in combination with nivolumab, an anti-programmed cell death protein (PD)-1 mAb, demonstrated greater efficacy than platinum-based standard regimen in first-line MPM patients, and it has very recently become the new standard of care in several countries[9].

This review critically discusses the recent strategies with immunotherapeutic approaches and those currently under investigation.

METHODS

A comprehensive search strategy of the currently available literature on PubMed, PMC, and NLM databases was performed to identify published studies involving immune checkpoint inhibitors (ICIs) and other immune-therapeutic approaches for the treatment of MPM patients. Furthermore, congress material from the most important oncology conferences held by international associations, including the American Society for Clinical Oncology (ASCO), the International Association for the Study of Lung Cancer (IASLC), the European Society for Medical Oncology (ESMO), and the International Mesothelioma Interest Group, were also evaluated.

Immuno-oncology: immune checkpoint inhibitors

Up to 2020, no treatments succeeded the platinum-pemetrexed combination regimen in association with or without bevacizumab as a first-line option for unresectable MPM[5,6,8].

Indeed, new effective therapeutic agents have been frustratingly slow to develop. This dramatic scenario has recently changed with the phase III CheckMate 743 trial[10], which showed a statistically significant improvement in survival with nivolumab plus ipilimumab compared to chemotherapy, thereby licensing this new regimen as the first choice for advanced MPM subjects in most countries. This approval followed a long course of clinical studies with CTLA-4/PD-1/PD-ligand(L)-1 blocking agents used alone or in combination showing signs of antitumor activity [Figure 1], mostly conducted in pretreated MPM patients, a setting in which therapeutic options are very limited[11,12].

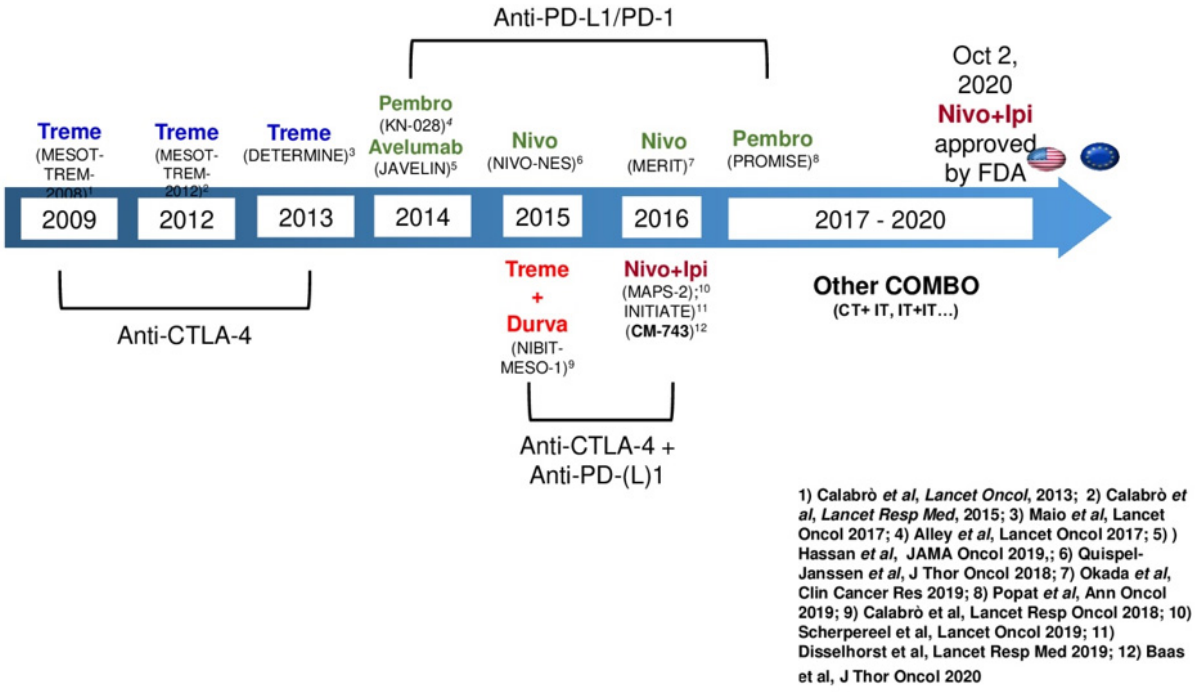

Figure 1. Selected most relevant studies with ICIs in mesothelioma patients.

Targeting CTLA-4

The phase II MESOT-TREM 2008 trial was the first study that opened the path towards this novel therapeutic approach. In this study, 29 pretreated MPM and peritoneal malignant mesothelioma patients underwent anti-CTLA-4 mAb tremelimumab therapy at the dose of 15 mg/kg every 90 days until disease progression or unacceptable toxicity. Although the primary endpoint was not reached due to the low ORR (6.9%), preliminary signs of antitumor activity were noted, in particular in terms of mOS which was 10.7 months[13]. Therefore, a second study, MESOT-TREM 2012, started. In this phase II trial, based on the pharmacokinetic analysis generated in previous studies[14], tremelimumab was given at the intensified dose of 10 mg/kg every four weeks for six cycles, followed by maintenance every 12 weeks. Opposite to MESOT-TREM-2008, in this study, the primary endpoint was reached with an immune-related ORR of 13.8%[15]. Moreover, the study showed a good safety profile, with grade 3-4 toxicity observed in only 7% of treated patients[15]. In light of these promising results, the phase IIb, placebo-controlled, double-blind DETERMINE study started. Overall, 568 patients affected by pretreated MPM or peritoneal malignant mesothelioma were randomized to receive tremelimumab, given at the same intensified dose utilized in the MESOT-TREM-2012 study, or placebo. Unfortunately, the primary endpoint was not reached: tremelimumab failed to demonstrate an improvement in OS, compared to placebo (7.7 and 7.3 months, respectively; HR = 0.92; $P = 0.41$)[16].

Targeting PD1/PDL1 axis

The development of a second generation of immunomodulating mAb directed against the PD-1/PD-L1 axis aroused keen interest to explore in MPM patients because of their more promising profile in efficacy and safety compared to that of anti-CTLA-4 mAb in different tumor types. Thus, various phase I/II trials were conducted in MPM patients[11,12,17-21]. Among the most representative studies, the phase Ib Keynote 028 study (NCT02054806) was conducted on 25 MPM patients treated with pembrolizumab. The results show a response rate of 20% and a mOS of 18 months[20].

In the MERIT II study, a flat dose of nivolumab administration (240 mg every two weeks) was evaluated in 34 Japanese pretreated MPM patients. The mOS was 17.3 months, three-year survival was 23.5%, mPFS was 6.1 months, and ORR was 29%, regardless of the histotype[21]. Because of these results, nivolumab received approval as second-line therapy for MPM patients in Japan[21].

Following these positive results, two phase III studies, PROMISE-Meso and CONFIRM, started[22,23]. In the first one, 144 unresectable, pretreated MPM patients were randomized to receive chemotherapy (gemcitabine or vinorelbine) or pembrolizumab. Crossover to pembrolizumab was allowed. After a median follow-up of 11.8 months, no differences were seen in mOS and mPFS between pembrolizumab and chemotherapy (mOS, 10.7 *vs.* 12.4 months; HR = 1.12; 95%CI: 0.74-1.69; $P = 0.59$; mPFS, 2.5 *vs.* 3.4 months; HR = 1.06; 95%CI: 0.73-1.53; $P = 0.76$)[21]. However, in the group treated with pembrolizumab, an increase in response rate was recorded (22% *vs.* 6% treated with chemotherapy, $P = 0.004$). The PD-L1 expression was not predictive of better survival with pembrolizumab[22].

In the CONFIRM trial, 332 second- or third-line MPM patients were randomized to receive nivolumab or placebo. In this trial, cross-over was not permitted. Median OS was slightly higher with nivolumab than in the placebo group (9.2 *vs.* 6.6 months; HR = 0.72; 95%CI: 0.55-0.94; $P = 0.018$)[23]. Opposite to CheckMate 743, an improvement in OS was seen in patients with epithelioid histology (9.4 *vs.* 6.6; HR = 0.71; 95%CI: 0.53-0.95; $P = 0.021$) but not in those with non-epithelioid histology (5.9 *vs.* 6.7 months; HR = 0.79; 95%CI: 0.35-1.79; $P = 0.572$)[8,22]. The grade 3 and 4 adverse event rates were 13.1% in the nivolumab arm and 2.7% in the placebo arm[23].

Although the results generated from these studies demonstrate an overall antitumor efficacy of CTLA-4 or PD-1/PD-L1 inhibition, the latter seems to be limited to a subgroup of subjects, probably because the immune-modulating effect of these agents may not be enough to overcome the strong immunosuppressive microenvironment of MPM if used as monotherapy.

Co-targeting of CTLA-4 and PD1/PDL1 axis

In the last few years, great efforts have been made on combination regimens targeting ICIs to enhance the efficacy of immunotherapeutic agents and overcome primary resistance to treatment observed in a large proportion of cancer patients. Several mechanisms of resistance have been thus far identified[24], and strategies to overcome them represent an area of strong investigation.

Along this line, co-targeting CTLA-4 and PD-1/PD-L1 axis represents an optimal combination regimen in view of a complementary mechanism of action of these molecules. Indeed, CTLA-4 and PD-1/PD-L1 molecules act in two different phases of T-cell activation; therefore, they are non-redundant and cooperative pathways. The antitumor efficacy of CTLA-4 and PD-1/PD-L1 blockade has been largely investigated and, recently, obtained approval for several cancer types, including microsatellite instability (MSI)-positive colorectal cancer (CRC), renal cell carcinoma, non-small cell lung cancer (NSCLC) (in combination with chemotherapy), and gastrointestinal cancer[25,26].

NIBIT-MESO-1 was the first study that investigated the potential efficacy of ICI combination regimens in mesothelioma patients. In this phase II study, 40 MPM or peritoneal mesothelioma patients received, in first or second line, tremelimumab at 1 mg/kg in combination with durvalumab at 20 mg/kg every four weeks for four cycles (induction phase), for non- progressor patients, followed by maintenance with only durvalumab, at the same dose, every 4 weeks for a maximum of nine cycles. Noteworthy, patients who experienced disease progression during the maintenance or follow-up phase were allowed to restart the

combination treatment. The study reached its primary endpoint with an immune-related objective response of 28%; the median duration of response was 16.1 months, DCR was 65%, and mOS was 16.5 months[27]. The three- and four-year OS rates were 20% and 15%, respectively[28]. Among the 40 patients enrolled in the NIBIT-MESO-1 study, 17 met the criteria for retreatment. Interestingly, 41% of retreated patients achieved a DCR; moreover, no grade 3-4 immune-related adverse events were observed[28]. Seeking to identify predictive biomarkers for patient selection to retreatment, an assessment of tumor mutational burden (TMB) was performed, and the results show a significantly (P = 0.02) higher mOS for retreated patients with a TMB over the median (41.3 months) compared with those who had a TMB level under the median one (17.4 months)[28].

Following the NIBIT-MESO-1 study, two additional combination trials have been conducted in MPM patients. In the IFCT-1501 MAPS-2 study, 54 patients received nivolumab plus ipilimumab. Overall, 12-week disease control was achieved by 32/62 patients (52%), the mOS was 15.9 months and 26% had grade 3-4 toxicities[29]. In the INITIATE study, 10/34 patients treated with ipilimumab plus nivolumab achieved a partial response (PR) and 13 (38%) had stable disease (SD); mOS was not reached at the time the analysis was performed. Grade 3-4 treatment-related adverse events were reported in 12 (34%) of 35 patients[30]. Table 1 summarizes the main clinical trials and results of ICI therapies.

The results generated from the NIBIT-MESO-1, MAPS-2, and INITIATE studies strongly contributed to the activation of the randomized, phase III CheckMate 743 trial[10]. In this study, 605 not pretreated MPM patients were randomized (1:1) to receive nivolumab, at the dosage of 3 mg/kg every two weeks, in combination with ipilimumab, at the dosage of 1 mg/kg every six weeks, for up to two years or the standard first-line treatment with platinum compound and pemetrexed combination for a maximum of six cycles. In the primary analysis, a statistically significant improvement in OS (the primary aim of the trial) was seen in the immunotherapy arm compared with the chemotherapy one, with a mOS of 18.1 *vs.* 14.1 months (HR = 0.74; P = 0.002). The benefit in OS was strongly relevant in patients with non-epithelioid histology treated with ICI, but this seems to be caused by the well-known less responsiveness of sarcomatoid subtype to chemotherapy. Additionally, in the experimental arm, there was no difference in median OS between patients with PD-L1 expression of < 1% and ≥ 1% (17.3 *vs.* 18 months), while, in the chemotherapy arm, median OS was statistically significantly longer in the first group than in the second one (16.5 *vs.* 13.3 months)[10]. A possible explanation could be a worse outcome of MPM expressing PD-L1 > 1% compared with those without PD-L1 expression. However, this exploratory analysis should be interpreted with caution because the study was not designed to demonstrate this suggestive hypothesis. Further studies are needed.

Although no significant differences were seen in median progression-free survival (PFS) and objective response rates (ORR) between the two arms, the median duration of response was significantly longer with combination immunotherapy (11.0 *vs.* 6.7 months). Grade 3 and 4 treatment-related adverse events were similar in the ICI (30%) and chemotherapy groups (32%). However, the incidence and severity of the adverse events led to a greater rate of discontinuation in the ICI group (15%) than in the chemotherapy group (7%), and three treatment-related deaths were reported in the ICI group compared with only one in the chemotherapy arm[10]. Concerning these latter aspects, the lesser experience of many oncologists in immune-related toxicity management might have contributed to this difference. In the ICI arm, the most frequent toxicities observed were dermatological, gastrointestinal, endocrine, hepatic, and pulmonary. Noteworthy, approximately 35% of patients who discontinued treatment with nivolumab and ipilimumab due to the onset of side effects had a persistent objective response and an improvement in mOS (25.4 months) compared to those observed in all patients treated with ICIs (18.1 months)[10]. Furthermore, nivolumab and ipilimumab combination improved disease-related symptoms and maintained QoL in

Table 1. Most representative clinical trials on ICIs alone or in combination

Regimen	Trial design	Patients (N°)	Results	Refs.
IPI-NIVO *vs.* Chemotherapy	Phase III Randomized 1st line	605	mOS 18.1 *vs.* 14.1 months; HR, 0.74; *P* = 0.002	[10]
IPI-NIVO *vs.* NIVO	Phase II Randomized 2nd and further line	125	mOS 15.9 *vs.* 11.9 months	[29]
IPI-NIVO	Phase II Not-Randomized 2nd and further line	34	SD 38%; mOS: not reached	[30]
Durvalumab plus chemotherapy	Phase II trial Single arm 1st line	55	Median OS: 21.0 months	[39]
Durvalumab plus chemotherapy	Phase II trial Single arm 1st line	55	6-month PFS: 57%	[40]
Durvalumab plus tremelimumab	Phase II trial Single arm 1st line or pretreated	40	Immune-related ORR: 28% DCR 65%; mOS: 16.5 months	[28]
NIVO	Phase II trial Single arm 2nd and further line	34	ORR: 29% mOS: 17.3 months	[12]
NIVO *vs.* Placebo	Phase II Randomized 2nd and further line	332	mOS 9.2 months *vs.* 6.6 months; HR: 0.72 1-year OS: 43.4% *vs.* 30.1%	[23]
Pembrolizumab *vs.* Institutional choice	Phase III Randomized 2nd and further line	144	mOS 10.7 months *vs.* 12.4 months; HR: 1.12; *P* = 0.59 ORR: 22% *vs.* 6% ; *P* = 0.004	[22]
Pembrolizumab	Phase Ib Single arm 2nd and further line	25	ORR 20%; mOS: 18 months	[20]
Tremelimumab	Phase II trial Single arm 2nd and further Line	29	ORR: 6.9% mOS: 10.7 months	[15]
Tremelimumab	Phase II trial Single arm 2nd and further line	29	Immune-related ORR: 13.8% (4 patients)	[13]
Tremelimumab *vs.* Placebo	Phase II Randomized 2nd and further line	571	mOS 7.7 months *vs.* 7.3 months; HR: 0.92; *P* = 0.41	[16]

NIVO: Nivolumab; IPI: ipilimumab DCR: disease control rate; DOR: duration of response; HR: hazard ratio; ICI: immune checkpoint inhibitor; MPM: malignant pleural mesothelioma; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.

patients with advanced MPM[31]. A three-year survival update showed a persistent benefit in survival for patients treated with ICI compared to those treated with chemotherapy (23% *vs.* 15%)[32]. The benefit was seen across subgroups including histology. Exploratory biomarker analyses demonstrated that a high score on a four-gene inflammatory signature (CD8A, STAT1, LAG3, and CD274) is correlated with better survival in the experimental arm than in the standard one[32]. The CheckMate 743 results led to the Food and Drug Administration (FDA) approval of nivolumab and ipilimumab combination in MPM patients in

October 2020, followed by the European Medicines Agency (EMA) approval in June 2021[33].

Is chemotherapy combined with ICI the next step?

Great efforts are currently addressing novel combination regimens to enhance the efficacy of immunotherapy and overcome primary resistance to treatment, largely observed in most cancer patients[34-38]. Along this line, chemotherapy could be an interesting partner for a combination regimen with immunotherapy, in view of its immunomodulatory properties. Currently, different trials investigating the efficacy of platinum-pemetrexed combined with ICIs are ongoing.

In the phase II PrE505 study, first-line MPM patients received treatment with platinum-pemetrexed in combination with the anti-PD-L1 durvalumab[39]. Updated results show a remarkable mOS of 20.4 months (95%CI: 13.0-28.5) with a one-year OS rate of 70.4%[39]. Furthermore, the study provided an interesting ORR of 56.4% (95%CI: 42.3-69.7%). In the phase II Dream study, patients were treated with a platinum-based regimen plus pemetrexed in combination with durvalumab used at the fixed dose of 1125 mg for six cycles, followed by durvalumab maintenance for up to one year. The study showed a six-month PFS rate of 57%[40]. Based on these promising results, the phase III Dream3r study is ongoing[41].

Two additional studies are currently ongoing: In the randomized, front-line phase III IND227 trial (NCT02784171), MPM patients receive platinum-based chemotherapy plus the anti-PD-1 pembrolizumab or chemotherapy alone. The study has completed the accrual, and the results are awaited. The actively recruiting phase III BEAT-Meso study s exploring the efficacy of chemotherapy plus bevacizumab and atezolizumab *vs*. only chemotherapy in first-line MPM patients (NCT03762018).

Results from the phase III studies are urgently awaited, and if positive, they could enrich the therapeutic approaches in this setting of disease.

Immune-oncology: not only ICI

Mesothelin (MSLN) is a membrane protein predominantly expressed in both normal and malignant mesothelial cells, above all in the epithelioid histological subtype. For these reasons, it appears to be an optimal candidate for targeted therapies[42]. The preliminary antitumor effect observed in preclinical studies led to the design of a phase I trial using T cells expressing a second-generation murine anti-mesothelin chimeric antigen receptor (CAR)[43,44]. No clinical response or "on target" toxicities were recorded, but interestingly an immunogenicity reaction to the murine SS1 scFv used in the CAR construct was noted[45]. Given these premises, a second phase I trial (NCT02159716) was conducted. Fifteen patients affected by different tumor types including mesothelioma received a lentiviral transduction vector expressing a second-generation murine-based anti-mesothelin CAR[46]. Cyclophosphamide was used as pretreatment to enhance CAR-T expansion. No complete responses (CR) or PR were reported, but a SD was found in 11/15 patients[46]. At the University of Pennsylvania, another trial is ongoing using both intravenous and intrapleural administration of a fully human anti-mesothelin CAR in combination with cyclophosphamide (NCT03054298). In a recently published phase I/II trial, mesothelin-targeting CAR-T cells were safely administered with an intrapleural injection to 31 patients, with no procedure-related adverse events greater than grade 1[47].

In another phase I/II trial, 25 pretreated MPM patients received an intrapleural administration of a MSLN targeting CAR T cell therapy either alone or followed by pembrolizumab[48]. Pembrolizumab was administered after CAR-T cell therapy in 18 patients. Promising results were observed, with an mOS of 23.9 months and a one-year OS of 83%[48]. Together with MSLN, fibroblast activation protein (FAP) and Wilms

tumor 1 (WT1) also represent promising targets for CAR-T cell therapies in MPM. FAP is highly expressed in the tumor microenvironment, particularly in cancer-associated stromal cells[49]. In a phase I trial, the anti-FAP CD8+ CAR-T cell intrapleural administration tested on three patients was safe (NCT01722149). No serious adverse events were reported[50,51]. WT1 is a protein expressed in both epithelioid and non-epithelioid MPM. An ongoing phase I/II trial using anti-WT1 TCR T cells in MM patients expressing WT1 and human leukocyte antigen (HLA)-A*0201 is ongoing. To increase their efficacy, central memory and naïve CD8+ T cells have been selected for TCR transduction (NCT02408016). Other promising targets tested in preclinical studies include MET[52], Pan-ErbB T4[53], 5T4[54], chondroitin sulfate proteoglycan 4 (CSPG4), and angiogenesis[55,56]. Therapeutic cancer vaccines represent another attractive therapeutic approach that aims to stimulate an antitumor immune response with the administration of engineered dendritic cells (DCs), genetic material, or peptides[57]. A long-lasting experience in DC vaccine has permitted the development of this approach in MPM. Based on promising preclinical results generated in mouse models[58], a phase I study with DC vaccine in MPM patients was conducted (NCT00280982). In the study, three patients (30%) obtained a partial response, and overall, the treatment showed a good safety profile[59]. In another phase I clinical trial, the autologous DC vaccine was combined with low-dose cyclophosphamide in 10 pretreated MPM patients (NCT01241682). The combination regimen showed a good safety profile and an antitumor effect in 7/10 patients, obtaining a survival of ≥ 2 years. After 50 and 66 months, 2 of 10 patients were alive[60]. Due to these impressive, although preliminary results, a phase II/III trial (NCT03610360) is ongoing. This trial is evaluating DCs loaded with allogeneic tumor cell lysates as maintenance therapy after first-line chemotherapy (DENIM trial), having OS as the primary endpoint[61].

An additional attractive study is the phase Ib MESOVAX (NCT03546426), i.e., investigating the efficacy of an autologous DC vaccine in combination with pembrolizumab in pretreated MPM or peritoneal mesothelioma patients. The study is currently recruiting.

Genetic vaccines, including DNA, RNA, and viral-based vaccines, aim to improve the antigen-specific antitumor immune response[62-67].

Several types of oncolytic viruses have been tested in various preclinical and clinical trials for the treatment of MPM[66,67]. Currently, a phase I clinical study is investigating the efficacy and safety of the intrapleural administration of an oncolytic measles virus (MV-NIS virus) in 15 MPM patients (NCT01503177).

WT1 is also considered as a potential target, not only for the development of CAR therapy but also for peptide vaccines in MPM patients[68]. In a randomized, phase II clinical trial (NCT01265433), pretreated MPM patients were randomized to receive analog WT1 peptide vaccine galinpepimut-S or placebo. The results show an increase in mPFS and mOS of 36% and 25%, respectively, in patients treated with the vaccine compared to the placebo group[69].

Based on these promising results, there is currently an ongoing phase I study (NCT04040231) investigating the safety of galinpepimut-S alone or in combination with nivolumab in pretreated MPM patients.

Additionally, in a phase I clinical trial (NCT01675765), the safety and efficacy of the sequential administration of CRS-207, an attenuated vaccine of *Listeria monocytogenes* genetically modified and engineered to stimulate an immune response against mesothelin (with or without cyclophosphamide) and chemotherapy, was investigated in MPM patients. The results demonstrate that CRS-207 administration is safe and the subsequent administration of cisplatin and pemetrexed is well tolerated. In particular, no patients developed listeriosis. Moreover, a PR was reported in 54% and a SD in 29% of patients enrolled;

mPFS and mOS were 7.5 and 14.7 months, respectively[70].

CONCLUSION

For decades, no progress whatsoever has been made in MPM, and many trials have failed to demonstrate the efficacy of new treatments[71]. A better knowledge of tumor biology and its interactions with immune cells and tumor microenvironment has recently led to a therapeutic paradigm shift in MPM, with the entrance to the clinic of the first chemotherapy-free regimen based on the association of nivolumab plus ipilimumab[10,72]. Based on this, immunotherapy is no longer regarded as "Cinderella" and has became the "Princess" therapy in MPM, giving new lifeblood to the clinical research on this tumor.

Certainly, much has to be gained to overcome the immune resistance to ICI; along this line, new ICI-based regimens or other agents such as anti-angiogenic compounds or cancer vaccines are currently under active investigation and will hopefully play a leading role in the treatment of mesothelioma[73,74].

Finally, the "one size fits all" approach is not recommended for patients with MPM; therefore, the identification of validated biomarkers is mandatory to select patients for the best treatment based on the characteristics of their tumor and the associated microenvironment.

DECLARATIONS

Acknowledgments

This work was partly supported thanks to the contribution of Ricerca Corrente by the Italian Ministry of Health within the research line L1P.

Authors' contributions

Wrote and revised the text: Bongiovanni A
Revised the text: Frassoldati A
Wrote and revised the text: Calabrò L
All authors provided comments on the initial version and approved the final draft of the manuscript.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Bongiovanni A. has served as advisor for Novartis/AAA and he has received funds from Amgen for a translational study. Frassoldati A. declare no conflict of interest; Calabrò L. has served as consultant or advisor to Bristol-Myers Squibb, Merck Sharp and Dohme, and received compensated educational activities from Bristol Myers Squibb, Astrazeneca, Sanofi.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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