Review Article

New horizons from immunotherapy in malignant pleural mesothelioma

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Abstract: Malignant pleural mesothelioma (MPM) is an aggressive disease with a severe prognosis. Medical treatment for MPM unresectable patients is still unsatisfactory; therefore novel therapeutic approaches are urgently needed. Immunotherapy represents a promising treatment for MPM patients. Here, we'll discuss the most promising immunotherapeutic treatments currently under active investigation for this still dreadful disease.

Keywords: Mesothelioma; immune-checkpoints; immunotherapy

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Introduction

Malignant pleural mesothelioma (MPM) is a fatal disease, mostly related to previous asbestos exposure (1). Its incidence is on the rise in the industrialized countries (2) and will reach its peak in the second to third decade of this century (3). The prognosis of MPM remains dismal because it is often diagnosed in an advanced stage of disease. Currently, an antifolate and platinum combination regimen represents the only established treatment for patients not amenable to curative surgery; however, this approach is largely unsatisfactory due to its limited impact on long-term survival of patients (4). Recently, a large randomized French study (MAPS) has shown that the addition of bevacizumab to cisplatin and pemetrexed results in an added benefit of 2.7 months in overall survival (OS) compared to standard therapy (5); however, this regimen is not yet considered a new standard of care in most countries. For patients who failed front-line chemotherapy the prognosis is even more dismal, as no standard second-line treatment has been yet defined (6). Among different therapeutic strategies largely investigated in MPM, immunotherapy represents a very promising approach (7). Indeed, spontaneous tumor-specific immune responses have been reported in MPM patients, and a better prognosis in patients with a high number of tumor-infiltrating immune cells has been demonstrated (8,9). In light of this evidence, a variety of clinical studies in the past explored the activity of different immunotherapeutic agents, in particular interferon- or interleukin-2-based regimens; unfortunately, these agents demonstrated limited efficacy or they were burdened with severe toxicity (10-13). A limited knowledge of multiple mechanisms of immune suppression operated by tumor cells, which include high levels of regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages in the tumor microenvironment, as well as non-appropriate methods for evaluating tumor response in the course of immunotherapy, could contribute, at least in part, to the failure of previous anti-tumor immunotherapeutic strategies (14).

In the recent years, a deeper understanding of the dynamic associations between pro-tumorigenic and anti-tumorigenic components of the MPM microenvironment and the interactions between tumor cells with host immune system have sparked new hopes to cure this disease with

immunotherapy (15,16). Along this line, a number of immunotherapeutic clinical trials, aimed at activating the host's immune system or overcoming components of the immunosuppressive tumor microenvironment, have been activated (17). Among these, the two main approaches of immunotherapy currently under investigation in MPM are focused on the targeting of immune-checkpoint inhibitors and mesothelin.

Immune checkpoint inhibitors

The remarkable progress in the clinical application of anti-tumor immunotherapy is mostly due to the development of therapeutic mAb (so-called immunomodulating mAb) targeting regulatory immune-checkpoints; these molecules are physiologically expressed on immune cells and play a crucial role in maintaining immune homeostasis and ensuring self-tolerance by mediating signals that attenuate excessive immune activation. Immunomodulating mAb restore and unleash anti-tumor activity of cytotoxic T cells by blocking inhibitor molecules on T cells or their ligand expressed on antigen presenting cells (APC) or tumor cells (18,19). This novel strategy has demonstrated its feasibility and efficacy in significantly prolonging long-term survival of patients with different malignancies in a large number of clinical studies, thus opening a new era in the history of cancer treatment.

Anti-cytotoxic T lymphocyte (CTLA)-4 mAb

CTLA-4 is a glycoprotein, member of the CD28 family receptors, inducibly expressed on the surface of activated CD4+ and CD8+ T cells, and constitutively expressed on regulatory T cells (19). CTLA-4 competes with CD28 costimulator receptor for the binding to ligand B7 (CD80 or CD86) expressed on APC; as CTLA-4 binds with higher affinity than CD28, it reduces CD28-dependent costimulation, and mediates direct inhibitory effects on the MHC-TCR pathway (19). Anti-CTLA-4 mAb by blocking CTLA-4 prevents its binding to B7, thus allowing T cells activation. Anti-CTLA-4 antibodies represent the prototype of this growing family of immunomodulating mAb targeting immune-checkpoints (19). Two anti-CTLA-4 mAbs are in clinical development: ipilimumab and tremelimumab. Ipilimumab represents the first of its class to demonstrate its ability to significantly improve the survival of metastatic melanoma patients (20), thus broadening its therapeutic exploration and prompting the clinical development of additional checkpoint blocking mAb in different tumor types, including malignant mesothelioma (MM) (21).

MESOT-TREM-2008 is the first study that explored the activity and safety of anti-CTLA-4 mAb in MM patients (22). In this phase II study, tremelimumab was administered at 15 mg/kg intravenous (IV) every 90 days in 29 second-line MM patients. Despite a low objective response rate (ORR) that was 7%, a long-lasting disease control and 2-year survival rate were observed in 31%, and 36% of MM patients, respectively (22). Additionally, grade 3–4 treatment-related side effects were observed in a minority of patients (22). These promising results were corroborated in the phase II MESOT-TREM-2012 study that investigated the activity and safety of tremelimumab in 29 additional second-line MM patients (23). In this second study, tremelimumab was given at an intensified dosing schedule of 10 mg/kg IV every 4 weeks (wks) for 6 doses, followed by administration of tremelimumab every 12 wks, based on previous pharmacokinetic data in metastatic melanoma patients (24). Four patients (14%) achieved an immune-related (ir)-ORR, thus the study reached its primary endpoint; among secondary endpoints explored, the ir-disease control rate (DCR) was 52%, the median duration of DCR was 10.9 months, and the median OS was 11.3 months; treatment was overall well tolerated, with grade 3–4 treatment-related toxicity observed in 7% of patients (23). These promising results contributed to the activation of a large, placebo controlled phase IIb study (DETERMINE); in this pivotal study tremelimumab was investigated in 571 second/third line MM patients at the same intensified schedule of administration utilized in the MESOT-TREM-2012 study (25). Unfortunately, the study did not show a superiority of tremelimumab for the primary endpoint of OS compared to placebo (25). Despite the failure of the study, this antibody class has had the merit of paving the way for the exploration of more effective immune checkpoint inhibitors, particularly those directed against programmed cell death protein (PD)-1 or its main ligand PD-L1 in this disease.

Anti-PD-1/PD-L1 mAb

PD-1 is a trans-membrane inhibitory immune-receptor, member of the B7-CD28 family, expressed on activated T, B, and natural killer cells (26). It binds to PD-L1 or PD-L2 that are expressed on stromal and tumor cells; these interactions lead to a reduction of cytotoxic T cells, release of cytokines, proliferation, and finally to a

depletion of T cells (26,27). Blocking PD-1 or PD-L1 by immunomodulating mAb, de-represses T cell activation, unleashing a clinical immune response towards the tumor (27). A growing number of anti-PD1/PD-L1 mAb has been recently approved in a variety of solid and hematological malignancies (28) thus prompting their investigation in additional tumor types including MPM.

The expression of PD-L1 has been reported in up to 60% of MPM samples in different series, with a higher rate in sarcomatoid histotype, and it has been associated to a poor prognosis (29-32). A growing number of phase I/II clinical studies with drugs targeting PD-1/PD-L1 axis are currently ongoing. In the phase Ib multi-cohort KEYNOTE-028 study, the anti-PD-1 pembrolizumab was investigated in PD-L1 positive pretreated MPM patients at a dose of 10 mg/kg every 2 wks (33). Five (20%) out 25 patients achieved a partial response (PR), and 13 (52%) a stable disease (SD); noteworthy, responses were durable with an average response duration of 12.0 months. Interestingly, the median progression free survival (PFS) was 5.4 months and the median OS was 18.0 months (33). The encouraging results observed in this first study prompted a rapid and large development of agents directed against the PD-1/PD-L1 axis in MPM. In a single-center phase II study, still ongoing at the University of Chicago (34), pembrolizumab was given in MPM and peritoneal MM patients at 200 mg every 3 wks; eligible patients were progressed to 1 or 2 prior regimens, and were unselected for PD-L1 status. Initial results reported an ORR of 21% and a DCR of 59%; median PFS was 6.2 months, and median OS was 11.9 months. Translational studies did not demonstrate a significant correlation between responses and PD-L1 expression or interferon-gamma gene expression profile (34). The activity of the anti-PD-1 nivolumab was investigated in the ongoing phase II NIVO-MES trial; 34 relapsed MPM patients received nivolumab at 3 mg/kg every 2 wks; preliminary data reported an ORR of 15%, regardless the PD-L1 expression on tumor cells, and a SD of 35%; median PFS was 3.6 months (35). In the phase II MERIT study, nivolumab was investigated at a flat dose of 240 mg IV every 2 wks in 34 second or third line MPM; results showed that 29.4% and 67.6% of patients reached an ORR and a DCR, respectively; in addition the PFS was 6.1 months and the median OS not reached at the time of that analysis (36). The role of nivolumab in pretreated MPM or peritoneal MM patients is currently being investigated in the randomized phase III double-blind, placebo-controlled CONFIRM study (37). In this study, patients progressed to at least two prior lines of chemotherapy are randomized in a 2:1 ratio to receive nivolumab at a flat dose of 240 mg or placebo. The trial has been recently opened in the United Kingdom, and will enroll 336 patients (37). In the phase Ib multicohort JAVELIN study, the anti-PD-L1 avelumab at the dose of 10 mg/kg every 2 wks was investigated in 53 MM patients progressing to at least one prior platinum/pemetrexed regimen (38). Patients were heavily pretreated, with a median of two prior treatments. A durable PR was observed in 5 (9%) patients; and an overall DCR was observed in 56% of patients. Median PFS was 17.1 wks, and the 24-week PFS was 38.4%. The most common treatment-related toxicity included fatigue, fever, infusion-related reactions, and dermatological side effects, similarly observed in trials with anti-PD-1 mAb (38).

Overall, these results indicate that targeting the PD-1/PD-L1 axis in MPM appears promising; however, these results have to be considered with caution because they are still very preliminary, and most of these trials are still ongoing. Therefore, several important issues regarding the role of these agents in MPM need to be further explored. Major efforts are currently directed to identify predictors of response to immune-checkpoint inhibitors, such as tumor molecular features or characterization of immune infiltrates in the tumor microenvironment, for a better patient selection for this therapeutic approach.

Combination strategy with immune-checkpoint blocking mAb

Though promising, the clinical benefit with PD-1/PD-L1 inhibitors is achieved by a limited proportion of MPM patients; to extend their benefit to a large population and to overcome primary or acquired immune-resistance observed in the majority of patients, current efforts are directed towards combined regimens.

Blocking of CTLA-4 could represent an optimal partner for combination regimen with PD-1/PD-L1 inhibitors; indeed these molecules act in two distinct phases of T cell activation; therefore, an additive or synergistic effect may be supposed by blocking these pathways. Consistently, evidence has shown a higher efficacy of nivolumab in combination with ipilimumab compared to nivolumab or ipilimumab alone in metastatic melanoma patients (39,40); along this line, a growing number of phase III clinical studies investigating the efficacy of combining CTLA-4 blockade with PD-1/PD-L1 blocking mAb are currently under investigation in different malignancies.

In the phase II NIBIT-MESO-1 study, the therapeutic potential activity of tremelimumab in combination with anti-PD-L1 mAb durvalumab was investigated in MPM and peritoneal MM patients (41). Forty patients received treatment with tremelimumab at a dose of 1 mg/Kg IV every 4 wks in combination with the anti-PD-L1 durvalumab at 20 mg/Kg IV every 4 wks for 4 doses during the induction phase, followed by durvalumab in monotherapy for additional 9 doses, in a maintenance phase. Primary endpoint of the study was to assess the ir-ORR in the study population; among secondary, were ir-DCR, ir-PFS, OS, and safety. The study is still ongoing but not recruiting. Safety analysis, was reported at ASCO meeting 2017, and demonstrated the tolerability of this combination regimen; indeed, most patients experienced mild or moderated ir toxicity (67.5%), and grade 3–4 treatment-related side effects were observed in 17.5% of patients; treatment-related toxicity was overall reversible according to protocol guidelines (41). Final efficacy analysis of NIBIT-MESO-1 study is currently ongoing.

In the phase II, randomized, non-comparative MAPS-2 study, nivolumab was investigated alone or in combination with ipilimumab in second or third line MPM patients. Final results have been recently shown at ASCO meeting 2017, and reported at week 12, a DCR of 44% or 50% with nivolumab alone or in combination with ipilimumab, respectively, thus the study reached its primary endpoint; among secondary endpoints explored, the median OS was 10.4 months with nivolumab alone, while it was not yet reached in the combo arm. Seventeen percent of patients experienced severe treatment-related side effects (42).

Several combination studies are currently ongoing, among these, the large, randomized, phase III Checkmate-743 study (NCT02899299) is currently investigating the efficacy of nivolumab in combination with ipilimumab in comparison to standard chemotherapy in first-line MPM patients; the Italian-Canadian phase III study is evaluating the efficacy of pembrolizumab alone or in combination with platinum-based regimen compared to chemotherapy alone in first-line MPM patients (NCT02784171). Additionally, a phase II study is exploring the immunological activity of durvalumab alone or in combination with tremelimumab in surgically resectable MPM (NCT02592551). Novel immune checkpoints are currently in early phase of clinical exploration in different tumor types; among these, in the phase I INDUCE-I study (NCT02723955), the safety and activity of GSK3359609 targeting the inducible T cell co-stimulator (ICOS), alone or in combination with pembrolizumab, is under investigation in selected advanced solid tumors including MPM. In *Table 1* the main ongoing trials with immune checkpoints blockade utilized alone or in combination with different agents are reported.

Immune-targeting of mesothelin

Mesothelin is a cell-surface glycoprotein, highly expressed in many solid tumors, including mesothelioma, with limited expression in normal tissues (43); therefore, it represents an optimal therapeutic target. Along this line, a variety of compounds for targeting of mesothelin with different mechanism of action are currently at various phases of clinical development; they mostly include chimeric mAb amatuximab, recombinant immunotoxins (SS1P, RG7787/LMB-100), antibody-drug conjugates (such as anetumab ravtansine), and chimeric antigen receptor (CAR)-T cells (44).

(I) Amatuximab is a mouse-human chimeric anti-mesothelin mAb; in a phase II study, it was investigated in combination with cisplatin and pemetrexed in MPM patients with promising results in median OS that was 14.8 months (45); therefore a randomized, phase II trial was launched but prematurely closed due to low accrual (46).

(II) Anetumab-ravtansine is an antibody-drug conjugate; after its binding with mesothelin expressed on tumor cells, the antibody-drug conjugate is internalized and releases the cytotoxic agent ravtansine (47). In a small phase Ib study, anetumab-ravtansine showed a response rate in pretreated MPM patients of 50%, and a DCR of 90%; unfortunately, in the subsequent randomized phase II study (47), this compound failed to demonstrate an improvement in survival in comparison to vinorelbine in second-line MPM patients (48,49).

(III) Recombinant immunotoxins: SS1P (anti-mesothelin dsFv-PE38) consists of a murine anti-mesothelin disulfide-stabilized single-chain Fv fragment (targeting moiety) linked to PE38 (effector moiety), the protein-synthesis-inhibiting domain of Pseudomonas exotoxin A (50). In phase I studies, SS1P generated neutralizing antibodies to the pseudomonas endotoxin (PE) (51,52); therefore, in a subsequent study, pentostatin and cyclophosphamide were given before the administration of SS1P to deplete T and B lymphocyte, thus delaying the

Table 1 Main studies with agents targeting immune checkpoints or mesothelin in MPM patients

Status	Study title	Interventions	Phase	Number enrolled	NCT number	Study start
Not recruiting	A Study of Tremelimumab Combined With the Anti-PD-L1 MEDI4736 Antibody in Malignant Mesothelioma (NIBIT-MESO-1)	Tremelimumab plus MEDI4736	Phase 2	40	NCT02588131	Oct 2015
Recruiting	A Phase 2 Study of Durvalumab in Combination With Tremelimumab in Malignant Pleural Mesothelioma	Tremelimumab; durvalumab	Phase 2	40	NCT03075527	Apr 2017
Recruiting	A Pilot Window-Of-Opportunity Study of the Anti-PD-1 Antibody Pembrolizumab in Patients With Resectable Malignant Pleural Mesothelioma	Pembrolizumab; cisplatin and pemetrexed	Phase 1	15	NCT02707666	Feb 2016
Active, not recruiting	Nivolumab Monotherapy or Nivolumab Plus Ipilimumab, for Unresectable Malignant Pleural Mesothelioma (MPM) Patients	Nivolumab; nivolumab + ipilimumab	Phase 2	125	NCT02716272	Apr 2016
Recruiting	Phase II MEDI4736 in Combination With Chemotherapy for First-Line Treatment of Unresectable Mesothelioma	Concurrent durvalumab; maintenance durvalumab	Phase 2	55	NCT02899195	Jun 2017
Recruiting	Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma	Cisplatin; pemetrexed; pembrolizumab	Phase 2	126	NCT02784171	Oct 2016
Recruiting	MEDI4736 Or MEDI4736 + Tremelimumab In Surgically Resectable Malignant Pleural Mesothelioma	MEDI4736; tremelimumab; untreated arm (control)	Phase 2	20	NCT02592551	May 2016
Not yet recruiting	Pembrolizumab With or Without Anetumab Ravtansine in Treating Patients With Mesothelin-Positive Pleural Mesothelioma	Anetumab ravtansine; pembrolizumab	Phase 1; phase 2	134	NCT03126630	Feb 2018
Active, not recruiting	Phase II Anetumab Ravtansine as 2nd Line Treatment for Malignant Pleural Mesothelioma (MPM)	Anetumab ravtansine (BAY 94-9343); vinorelbine	Phase 2	248	NCT02610140	Dec 2015
Active, not recruiting	Safety and Efficacy of Listeria in Combination With Chemotherapy as Front-line Treatment for Malignant Pleural Mesothelioma	Immunotherapy plus chemotherapy; immunotherapy with cyclophosphamide plus chemotherapy	Phase 1	60	NCT01675765	Aug 2012
Recruiting	CheckpOiNt Blockade For Inhibition of Relapsed Mesothelioma	Nivolumab; placebo	Phase 3	336	NCT03063450	Mar 2017
Recruiting	Study of Nivolumab Combined With Ipilimumab Versus Pemetrexed and Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma Patients	Nivolumab; ipilimumab; pemetrexed	Phase 3	600	NCT02899299	Oct 2016

Table 1 *(continued)*

Table 1 *(continued)*

Status	Study title	Interventions	Phase	Number enrolled	NCT number	Study start
Recruiting	Ipilimumab and Nivolumab in the Treatment of Malignant Pleural Mesothelioma	Nivolumab and ipilimumab	Phase 2	33	NCT03048474	Sep 2016
Not yet recruiting	PembrolizuMab Immunotherapy Versus Standard Chemotherapy for Advanced prE-treated Malignant Pleural Mesothelioma	Pembrolizumab; gemcitabine; vinorelbine	Phase 3	142	NCT02991482	Sep 2017
Recruiting	Pembrolizumab in Treating Patients With Malignant Mesothelioma	Pembrolizumab	Phase 2	65	NCT02399371	Mar 2015
Not yet recruiting	Atezolizumab, Pemetrexed Disodium, Cisplatin, and Surgery With or Without Radiation Therapy in Treating Patients With Stage I-III Pleural Malignant Mesothelioma	Atezolizumab; cisplatin	Phase 1	28	NCT03228537	Nov 2017
Recruiting	Evaluation of CRS-207 With Pembrolizumab in Previously Treated MPM	CRS-207; pembrolizumab	Phase 2	35	NCT03175172	Jun 2017
Recruiting	Study of FAK (Defactinib) and PD-1 (Pembrolizumab) Inhibition in Advanced Solid Malignancies (FAK-PD1)	Defactinib; pembrolizumab	Phase 1; phase 2	59	NCT02758587	Jul 2017
Recruiting	A Study of the Safety, Tolerability and Pharmacokinetics of ABBV-368 as a Single Agent and Combination in Subjects With Locally Advanced or Metastatic Solid Tumors	ABBV-368; nivolumab	Phase 1	100	NCT03071757	Apr 2017
Not yet recruiting	INCAGN01876 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies	INCAGN01876; epacadostat; pembrolizumab	Phase 1; phase 2	166	NCT03277352	Oct 2017
Not yet recruiting	A Study Exploring the Safety and Efficacy of INCAGN01949 in Combination With Immune Therapies in Advanced or Metastatic Malignancies	INCAGN01949; nivolumab; ipilimumab	Phase 1; phase 2	651	NCT03241173	Oct 2017
Recruiting	Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01876 Combined With Immune Therapies in Advanced or Metastatic Malignancies	INCAGN01876; nivolumab; ipilimumab	Phase 1; phase 2	450	NCT03126110	Apr 2017
Recruiting	Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158)	Pembrolizumab	Phase 2	1350	NCT02628067	Dec 2015
Recruiting	Dose Escalation and Expansion Study of GSK3359609 in Subjects With Selected Advanced Solid Tumors (INDUCE-1)	GSK3359609 IV infusion; pembrolizumab 200 mg IV infusion	Phase 1	304	NCT02723955	Jun 2016

Table 1 *(continued)*

Table 1 *(continued)*

Status	Study title	Interventions	Phase	Number enrolled	NCT number	Study start
Recruiting	Adjuvant Pembrolizumab After Radiation Therapy for Lung-Intact Malignant Pleural Mesothelioma	Hemithoracic radiation; therapy palliative; radiation therapy; pembrolizumab	Phase 1	24	NCT02959463	May 2017
Not yet recruiting	Atezolizumab, Pemetrexed Disodium, Cisplatin, and Surgery With or Without Radiation Therapy in Treating Patients With Stage I-III Pleural Malignant Mesothelioma	Atezolizumab cisplatin; extrapleural; pneumonectomy	Phase 1	28	NCT03228537	Nov 2017
Recruiting	Mesothelin-Targeted Immunotoxin LMB-100 in People With Malignant Mesothelioma	LMB-100; nab-paclitaxel	Phase 1	34	NCT02798536	Jun 2016
Active, not recruiting	Safety and Effect of GL-ONC1 Administered IV Prior to Surgery to Patients With Solid Organ Cancers Undergoing Surgery	GL-ONC1	Phase 1	36	NCT02714374	Mar 2016
Recruiting	Re-directed T Cells for the Treatment (FAP)-Positive Malignant Pleural Mesothelioma	Adoptive transfer of re-directed T cells	Phase 1	6	NCT01722149	Oct 2014
Active, not recruiting	SS1P and Pentostatin Plus Cyclophosphamide for Mesothelioma	Pentostatin; cyclophosphamide; SS1(dsFv)PE38-lot 073I0809; SS1(dsFv) PE38-lot FIL129J01	Phase 1; phase 2	55	NCT01362790	May 2011
Recruiting	A Randomised Phase II Open-label Study With a Phase Ib Safety lead-in Cohort of ONCOS-102, an Immune-priming GM-CSF Coding Oncolytic Adenovirus, and Pemetrexed/Cisplatin in Patients With Unresectable Malignant Pleural Mesothelioma	ONCOS-102; pemetrexed/cisplatin; cyclophosphamide	Phase 1; phase 2	30	NCT02879669	Jun 2016
Recruiting	A Randomised Phase II Open-label Study With a Phase Ib Safety lead-in Cohort of ONCOS-102, an Immune-priming GM-CSF Coding Oncolytic Adenovirus, and Pemetrexed/Cisplatin in Patients With Unresectable Malignant Pleural Mesothelioma	ONCOS-102; pemetrexed/cisplatin; cyclophosphamide	Phase 1; phase 2	30	NCT02879669	Jun 2016
Recruiting	αDC1 Vaccine + Chemokine Modulatory Regimen (CKM) as Adjuvant Treatment of Peritoneal Surface Malignancies	DC vaccine; celecoxib; interferon Alfa-2b; rintatolimod	Phase 1; phase 2	168	NCT02151448	Jul 2014
Recruiting	CAR T Cell Receptor Immunotherapy Targeting Mesothelin for Patients With Metastatic Cancer	Fludarabine; anti-mesothelin CAR; cyclophosphamide; aldesleukin	Phase 1; phase 2	136	NCT01583686	Apr 2012

Table 1 *(continued)*

Table 1 *(continued)*

Status	Study title	Interventions	Phase	Number enrolled	NCT number	Study start
Recruiting	CAR T Cells in Mesothelin Expressing Cancers	Hu-CART meso cells	Phase 1	30	NCT03054298	Mar 2017
Recruiting	Phase Ib Study of Anetumab Ravtansine in Combination With Pemetrexed and Cisplatin in Mesothelin-expressing Solid Tumors	BAY 94-9343; pemetrexed; cisplatin	Phase 1	30	NCT02639091	Feb 2016
Unknown	Dendritic Cells Loaded With Allogeneous Cell Lysate in Mesothelioma Patients	MesoCancerVac	Phase 1	9	NCT02395679	Jan 2015
Recruiting	Autologous Dendritic Cell Vaccination in Mesothelioma	Dendritic cell vaccination plus chemotherapy	Phase 1; phase 2	20	NCT02649829	Aug 2017
Unknown	A multi-centre, open-label, uncontrolled, phase II study to investigate efficacy and safety of ONO-4538 in malignant pleural mesothelioma	ONO-4538	Phase 2	34	JapicCTI-No.163247	Jul 2016

MPM, malignant pleural mesothelioma.

development of neutralizing antibodies; initial signs of activity were observed in 3/10 patients treated in a phase I study (53). To minimize immunogenicity, Hollevoet *et al.* re-engineered the targeting moiety from mouse dsFv to humanized Fab and de-immunized the effector moiety PE to generate a new immunotoxin, called RG7787/LMB-100 (54). A phase I study to assess the maximum tolerated dose and the immunogenicity of RG778 is currently under way in MPM patients (NCT02798536).

(IV) Mesothelin CARs: adoptive T cell therapy using engineered T cells directed towards tumor antigens (CAR-T) is another promising approach that has shown impressive clinical outcomes in leukemia, and it is now being investigated in solid malignancies (55). Mesothelin is an especially appealing target for this approach since it is overexpressed in the majority of MPM, and several preclinical and clinical studies have found that is involved in tumorigenesis, as well as being associated with tumor aggressiveness (56). Data generated in CAR-T cells, mainly directed against mesothelin in MPM patients, demonstrated early signs of clinical activity and T cell reactivity towards the tumor. Mesothelin CARs are currently being investigated in multiple phase I clinical trials (NCT02414269, NCT01583686, NCT02580747, NCT02159716, and NCT01355965). Further adaptations of the CAR-T cell strategy, including intrapleural delivery approaches, are under investigation to increase tumor infiltration and decrease treatment-related side effects (57).

Other immunotherapeutic approaches

Additional immunotherapeutic strategies, including vaccines (such as CRS-207, a Listeria monocytogenes expressing human mesothelin), intrapleural administration of an adenovirus expressing interferon alpha (Ad.IFN-α), vaccination with a Wilms' tumor-1 (WT-1) peptide analogue, dendritic cell vaccine, are currently under investigation in early phases of clinical studies (44). *Table 1* reports the currently ongoing main trials, investigating the activity and safety of these therapeutic approaches.

Future directions/perspectives

Much has to be gained in the therapeutic scenario of MPM: the heterogeneity and the relatively low incidence of this disease, together with the difficult radiological evaluation of tumor response in MPM patients, particularly in the course of treatment with immunotherapeutic agents, pose barriers to developing more effective systemic therapies. However, in the last decade, a significant growth in the knowledge

of mesothelioma immune-biology has translated into the development of a variety of novel immunotherapeutic agents that are beginning to show clinical potential in MPM patients. Targeting immune-checkpoint inhibitors and mesothelin, including combinations of these novel agents, appear to be among the most encouraging of the emerging therapeutic approaches.

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