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MESOTHELIAL CELLS REGULATE IMMUNE RESPONSES IN HEALTH AND DISEASE: ROLE FOR IMMUNOTHERAPY IN MALIGNANT MESOTHELIOMA

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Abstract

The mesothelium was first described by Bichat in 1827 and originally thought to function purely as a non-adhesive surface to facilitate intracoelomic movement of organs. However, the mesothelium is now recognised as a dynamic cellular membrane with many important functions that maintain serosal integrity and homeostasis. For example, mesothelial cells interact with and help regulate the body's inflammatory and immune system following infection, injury or malignancy. With recent advances in our understanding of checkpoint molecules and the advent of novel immunotherapy approaches, there has been an increase in the number of studies examining mesothelial and immune cell interaction, in particular the role of these interactions in malignant mesothelioma. This review will highlight some of the recent advances in our understanding of how mesothelial cells help regulate serosal immunity and how in a malignant environment the immune system is hijacked to stimulate tumor growth. Ways to treat mesothelioma using immunotherapy approaches will also be discussed.

Highlights:

- Mesothelial and immune cell interactions play a crucial role in tissue homeostasis in the serosal cavities such as the pleura.
- Mesothelin is viewed as an attractive target for solid tumors, including malignant mesothelioma.
- Checkpoint inhibitor therapy has shown variable efficacy against malignant mesothelioma.
- CAR T cell therapies are being evaluated for malignant mesothelioma.
- Treatment of malignant mesothelioma will require multimodality approaches with immunotherapy central to future therapeutic approaches.

Introduction

The mesothelium consists of a single layer of cells that lines the three coelomic cavities; pleura, peritoneum and pericardium. It plays important roles including providing a barrier and first line of defense against infectious agents [1]. Mesothelial cells have a well-developed surface glycocalyx which repels foreign cells and organisms, and they are bathed in serosal fluid containing immunoglobulins, complement, lysozyme and other proteins to protect the mesothelial barrier from pathogens. Mesothelial cells have an immunoregulatory role, which is achieved through expression of multiple pattern recognition receptors that activate innate immune responses. In addition, they secrete several chemokines and cytokines that coordinate leukocyte migration to the site of inflammation and are able to present antigens to T cells [2]. However, interactions between mesothelial cells and immune cells can also drive pathological processes such as malignant mesothelioma (MM). This review will highlight some of the most recent studies examining mesothelial-immune cell interactions and how these might be modulated by immunotherapeutic intervention to treat MM.

Immune cell interaction with mesothelial cells

The pleural space is a sequestered local environment formed by mesothelial cells joined by junctional complexes, including tight junctions [3]. Tight junctions are important to help maintain a permeability barrier that restricts cell and fluid movement across the serosa. Mesothelial cells regulate both innate and adaptive immune responses at the serosal surface. They express multiple pattern recognition receptors (PRRs) that recognize different carbohydrates and lipopolysaccharide moieties on the surface of microbial pathogens and release mediators to initiate inflammation and activate immunomodulatory pathways. Mesothelial cells also recognize molecules derived from the host including cytokines, heat shock proteins, nucleic acids, ATP and HMGB1 that are released in response to tissue damage [4]. In response to these signals, mesothelial cells secrete a range of mediators such as antimicrobial peptides[5], chemokines and

inflammatory cytokines such as tumor necrosis factor alpha, interleukin (IL)-1, IL-6, and IL-8 and interferons, which in turn directs the differentiation of T cell subsets such as Th1, Th2, Th17 or regulatory T cells [6,7].

The pleura is also a common site of metastasis for many tumor types and is the primary site for the development of malignant mesothelioma (MM). Tumor growth is often accompanied by the formation of pleural effusions, which are accumulations of serous fluid rich in tumor cells, mesothelial cells, immune cells and the cytokines, growth factors, chemokines and other mediators these cells secrete. This fluid in turn provides an immunosuppressive environment which supports tumor growth [8].

Immune hallmarks of Mesothelioma

Chronic inflammation is a cancer risk and inflammation in tumors increases cancer progression. The tumor microenvironment secretes chemokines and growth factors that recruit tumor infiltrating lymphocytes (TILs) to facilitate tumor growth [9]. MM, which is strongly associated with asbestos exposure and fiber-associated inflammation, can form on any serosal surface. However, malignant pleural mesothelioma (MPM) is the most common. There are three histological types of MM; epithelioid, sarcomatoid and biphasic (a mix of epitheliod and sarcomatoid) [10,11]. Epithelioid MM is associated with high levels of TILs while sarcomatoid MM is associated with immune unresponsiveness or active immune suppression through recruitment of CD4+ Tregs and regulatory B cells (Bregs) expressing the inhibitory checkpoint marker PD-1 and its ligand PD-L1 [11] (Figure 1). MM is often unresponsive to treatments such as chemotherapy and radiotherapy [12]. Therefore, there is growing interest in understanding the detailed cellular composition of the inflammatory tumor microenvironment of individual patients to help develop new therapeutic approaches. The composition and behavior of immune cells can

vary from the peripheral blood to the tumor tissue or within effusions, which are used to study tumor-specific immune cell populations [13,14].

Normal human mesothelial cells and MPM tumor cell lines can secrete IL-6, IL-8, colony stimulating factor (CSF)-1, CSF-2 and monocyte chemoattractant protein (MCP)-1, which facilitate the recruitment of monocytes from the bone marrow or spleen to the tumor site where they undergo differentiation into tissue macrophages [15,16]. Tumor associated macrophages (TAMs) establish an immunosuppressive environment through the secretion of transforming growth factor beta (TGF-β), IL-10, chemokine ligand (CCL)17 and CCL22 [17,18]. The elevated levels of TGF-β and IL-10 within the tumor environment directs the polarization of macrophages toward the M2 "alternatively activated" phenotype that function in tissue remodeling and immune regulation [17]. The accumulation of TAMs is associated with a poor prognosis across a range of cancers including MPM [19,20]. Interestingly non-epithelioid MPM tumors, which have a poorer prognosis, contain significantly higher levels of TAMs expressing markers consistent with an M2 phenotype [21].

The major lymphocyte populations that infiltrate tumors include CD4+ and CD8+ T cells and B cells [22,23]. CD4+ TILs include immunosuppressive CD4+ Tregs that antagonize proliferation and function of tumor-specific CD8+ cytotoxic T (Tc) cells [24,25]. The tumor microenvironment may contain high levels of TGF-β, which promotes differentiation of M2 macrophages and CD4+ Tregs that inhibit CD8+ TILs effector functions [14,26]. Tazzari and colleagues showed that epithelioid tumors had reduced CD4+ Th1 immune responses and increased recruitment of CD4+ Tregs [11]. Depletion of CD4+ Tregs from tumor tissues including MPM has been shown to have beneficial effects, which allow CD8 TIL effector functions to be resumed. Experimental treatments using anti-CD25 immunotoxin [27] or animal models that allow conditional depletion of Tregs *in vivo* by administration of a diphtheria toxin, allow CD8+ TILs to infiltrate the tumor

and reduce tumor volume to induce remission [28,29]. Removal of CD4+ Tregs from the tumor environment allow dendritic cells (DCs) to stimulate anti-tumor immunity driven by CD8+ TILs [28].

Checkpoint immunotherapy and mesothelioma

Tumor immunotherapy utilizing checkpoint inhibitors is increasingly used to treat solid tumors, including lung cancer [30], and is viewed as a potential effective treatment for MM (Table 1) [31-33]. Checkpoint inhibitors are antibody therapies that target specific cell surface markers associated with activated T cells, including PD-1 and CTLA-4 (Figure 1). PD-1 is expressed by chronically activated or "exhausted" T cells and CTLA-4 is an inhibitory receptor expressed by activated CD4+ and CD8+ T cells. Tumor cells express the PD-1 ligands, PD-L1 and/or PD-L2, while antigen presenting cells, DCs, macrophages and B cells, express the CD80 and CD86 costimulatory receptors that bind CTLA-4. Engagement of PD-1 and CTLA-4 on activated CD8+ T cells inhibits their proliferation and function, which enables tumors to evade immune detection. By targeting PD-1 or CTLA-4 on tumor CD8+ T cells, checkpoint inhibitors "reawaken" them from the exhausted phenotype so they will attack and eliminate the tumor.

Currently about 30% of patients receiving checkpoint inhibitor immunotherapy show a beneficial response [34]. In the MERIT study, a phase II MPM trial evaluating the PD-1 inhibitor nivolumab, 29% of patients had an objective response, consistent with most other tumor types [33]. A current phase II trial is testing the efficacy of nivolumab in relapsed MPM (CONFIRM, NCT03063450) [35]. The anti-PD-1 drug pembrolizumab has been evaluated in various phase trials (KEYNOTE) as second or third-line treatment. However after promising initial results, the phase III PROMISE-meso trial comparing pembrolizumab with a single-agent chemotherapy failed to show an improved median overall survival (OS) and progression-free survival (PFS), despite a superior

overall response rate (ORR) for pembrolizumab compared to chemotherapy alone [36]. Hassan and colleagues [37] reported the efficacy of treating MM patients with avelumab in the phase 1 JAVELIN solid tumor trial. Avelumab is a human anti PD-L1 antibody with a wild type Fc region capable of inducing significant anti-tumor activity via antibody dependent cellular cytotoxicity due to activation of adaptive and innate immune effector cells. The objective response rate was only 9%. In patients with PDL-1 positive tumors, the overall response rate was 19% and 6 month PFS was 27.5%, while the 12 month overalls survival rate was 72.5% with a median of 20 months. Tremelimumab, an anti-CTLA-4 therapy, has been very disappointing demonstrating no benefit over placebo (DETERMINE) as first, second or third-line treatment [38,39].

Given the modest success of anti-CTLA-4 and anti-PD-1 therapy in MPM trials, other immune checkpoint molecules, including V-domain Ig suppressor of T cell activation protein (VISTA), T cell immunoglobulin 3 (TIM3), OX40 and glucocorticoid-induced tumor necrosis factor receptor (GITR) could be considered for therapeutic targeting. VISTA was recently shown to be expressed in a large number of MM tumors, which correlated with better survival outcomes [40]. VISTA was more highly expressed on epithelioid and biphasic MPM whereas PD-L1 was more highly expressed on sarcomatoid MPM [40]. The VISTA molecule is structurally similar to PD-L1 and, when overexpressed, suppresses early T-cell activation and proliferation and reduces cytokine production [41]. One VISTA inhibitor, CA-170, is currently in clinical trial and is being evaluated in solid tumors and lymphomas NCT02812875, but it is unclear if MM is one of the tumor types being examined. Another VISTA inhibitor, JNJ61610588, was also being trialed in solid tumors but this trial was unfortunately terminated for business reasons. T cells activated via OX-40 or GITR display enhanced cell proliferation and survival and can overcome the inhibitory effects of Treg cells. TIM3 is an inhibitory molecule expressed on T cells and on a dysfunctional population of CD8+ T cell effectors, such as in tumors. In an animal model of MM, Fear and colleagues

showed a synergistic effect between anti-CTLA-4 and anti-OX40 to inhibit tumor growth [42]. We wait to see if this outcome is replicated in patients with MM.

Although checkpoint inhibitors have been used successfully in a variety of tumor settings, some patients develop adverse events such as interstitial pneumonia or pneumonitis. Identification of patients who will respond to checkpoint inhibitor therapy and those who will not or have adverse effects, is currently a major focus of immunotherapy research. In the MERIT study it was noted that tumors with >1% PD-L1 staining were more likely to have a beneficial response compared to those patients whose tumors had <1% staining of PD-L1 [10,33]. Unfortunately, as in every tumor type, expression of the checkpoint molecules does not correlate to response rate. Clearly, we do not fully understand the mechanism by which checkpoint inhibitors regulate tumor growth. Clinical trials have evaluated the use of combined therapies utilizing two inhibitors, but dual blockade still only provides a beneficial response of about 30% in most cases. Therefore, to improve the outcome of checkpoint immunotherapy, it is likely that it should be used in combination with surgery, chemotherapy, signaling inhibitors and other immune approaches such as CAR T cell and immunotoxin therapies.

CAR T cell therapy and mesothelioma

Chimeric antigen receptor (CAR)-T cell therapies are a new generation of immunotherapies that offer hope to cancer patients resistant to normal standard care therapies (Figure 2) [43,44]. CAR-T cells are T cells engineered to express a chimeric receptor that targets a tumor cell surface protein, carbohydrate or glycolipid [45]. CAR-T cells were first developed to treat B cell leukemias as they were constructed to express a chimeric receptor specific for CD19, a cell surface protein expressed abundantly on mature B cells. CD19 CAR-T cells have been used very effectively to treat acute lymphoblastic leukemias [43,44]. Second generation CAR-T cells are capable of targeting the tumor antigen and co-stimulating conventional T cells [46]. CAR receptors are currently designed

to express a single chain variable fragment (scFv) highly specific for the target antigen linked to a cytoplasmic signaling module (e.g. CD3ζ and costimulatory domain from CD28 or 41BB) [43,47]. High affinity for the target antigen can be problematic as it can also lead to dangerous reactivity against healthy organs or tissues that express the target antigen at low levels [43,47]. This has led scientists to try different approaches to enhance the safety and specificity of CAR-T cells.

The new generations of CAR-T cells under development are designed to target solid tumors such as MM. Mesothelin (MSLN) is a membrane-anchored glycoprotein normally expressed on mesothelial cells but is highly expressed in cancers including MM, pancreatic cancer, ovarian cancer, lung adenocarcinoma, gastric cancer and many others [45,48]. MSLN expression is stimulated by highly sulfated heparan sulphate proteoglycan (HSPG)-Wnt/β-catenin signaling, which occurs in many cancers [49], and Wnt signaling is potentiated in MM [50]. Furthermore, sulfatase-1, which has a tumor suppresser function by inhibiting Wnt signaling as well as other important tumor-related signaling pathways, is often downregulated in cancer and this leads to upregulation of MSLN [51].

In a mouse model of MPM, mice were treated either by systemic or intra-pleural mesothelin-specific CAR-T cells, which were long lived as they eradicated MM tumors 200 days after the initial tumor exposure [52]. Interestingly, CAR-T cells delivered via the intrapleural route displayed greater tumor control than those delivered systemically, as evidenced by increased T cell proliferation, T cell migration to metastatic sites, reduction in tumor volume and survival [52]. MSLN CAR-T cells that were engineered to express a single-chain variable fragment derived from the mouse monoclonal anti-MSLN antibody SS1 fused to the intracellular signaling domains of 4-1BB and CD3ζ, have recently been used in a phase 1 MM study [53]. They were expanded in the blood of patients and were well tolerated but there was limited clinical activity.

Several clinical trials with MSLN-specific CAR-T cells are currently underway in a range of cancers and we await the results to see how effective these cells can be against the various tumor types [46]. One problem with using CAR-T cells is that they are introduced into an immunosuppressive tumour environment. Adenosine, a metabolite that is highly produced in this environment, binds and signals through the adenosine 2a receptor (A2aR), which is expressed at the surface of activated T cells. This leads to enhanced production of intracellular cyclic AMP, which can attenuate anti-tumor T cell responses. Masoumi and colleagues recently showed that if they used shRNA knock down to inhibit the expression of *A2aR* gene in MSLN-CAR-T cells, they could reverse the effects of adenosine signaling leading to enhanced proliferation, cytokine production and cytotoxic functions of MSLN-CAR T cells *in vitro* [54]. Interestingly, pharmacological inhibition of A2aR enhanced MSLN-CAR-T cell proliferation and cytokine production but failed to rescue their cytotoxic function. Use of knockdown approaches to reduce A2aR needs further development but could be a promising approach to improve clinical outcomes.

Mesothelin-targeted therapies

MSLN is an attractive target for cancer therapy with antibody-based approaches as well as tumor vaccines. For example, MSLN binds to the ovarian cancer antigen MUC16 and induces cell-to-cell adhesion in these cells [55]. MUC16 expressed on cancer cells can also facilitate cancer cell attachment to MSLN expressed on mesothelial cells, possibly contributing to peritoneal seeding and metastatic spread of tumors [56]. Signaling via MSLN and MUC16 can increase resistance to anoikis [57], increase expression of metalloproteinases that are linked to cell invasion and metastasis [58-60] and can induce the secretion of cytokines to promote tumor growth [61,62].

A number of MSLN-specific antibody based therapeutic agents have been evaluated through clinical trials in various cancer settings. The therapeutic agents include anti-MSLN immunotoxins, chimeric anti-MSLN antibody, MSLN-directed drug conjugates and a live attenuated Listeria vaccine that expresses MSLN. A mesothelin cancer vaccine, CRS207, incorporates a recombinant live-attenuated *Listeria monocytogenes* (LADDLm) engineered to secrete MSLN into the cytosol of infected antigen presenting cells to facilitate priming of MSLN-specific CD8+T cells [63]. MM patients received two priming doses of the CRS207 vaccine followed by chemotherapy with pemetrexed/cisplatin. Improved progression free survival and overall survival were seen and a reduction in tumor size was observed post CRS207 infusion prior to chemotherapy, suggesting anti-tumor responses had been induced following vaccination. This was reflected in changes observed in tumor biopsies with an increase of the CD8+: Treg ratio, increased reinvigoration and proliferation of T cells and a shift from M2 to M1 macrophage phenotypes [64]. Unfortunately, a subsequent phase II trial (NCT03175172) showed no clinical activity of CRS-207 when combined with pembrolizumab (PD-1 inhibition).

Anetumab Ravtansine, previously called BAY 94-9343, an antibody-drug conjugate of anti-MSLN antibody linked to a tubulin inhibitor maytansinoid DM4, was compared with vinorelbine in patients with advanced MPM. Anetumab Ravtansine failed to improve progression free survival compared with vinorelbine [65]. However, Hassan and colleagues recently reported the results of a phase 1 study of Anetumab Ravtansine with advanced or metastatic solid tumors, including MPM. The drug was safe and showed encouraging preliminary anti-tumor activity in those patients with high levels of tumor MSLN expression. Phase II studies are currently planned [66].

BMS-986148 is a MSLN antibody conjugated to tubulysin, which causes cell death after internalization by target cells. In a phase 1/2a trial in patients with advanced solid tumors, including MPM (BMS-986148), alone or in combination with nivolumab, showed modest clinical

activity in patients but caused significant adverse events [67]. Amatuximab (MORAb-009) is a chimeric monoclonal antibody consisting of the SS1 scFv fused to the human IgG1 and κ constant regions. Trials in MPM and other MSLN-positive tumors showed limited clinical effects [68]. Other anti-MSLN-conjugated drugs, including BAY2287411 (NCT03507452) and HPN536 (NCT03872206), are currently undergoing testing for multiple tumor types including MM.

Immunotoxin agents that conjugate anti-MSLN antibodies to Pseudomonas exotoxin such as LMB-100 (NCT02798536, NCT04034238, NCT03644550), have also been assessed in MPM and other MSLN-expressing tumor types, and are progressing through clinical trials.

It is interesting to speculate why MSLN has been so frequently chosen as a cancer target given that it is expressed widely on mesothelial cells on healthy tissues. Analysis of the *MSLN* knockout mouse showed no discernible tissue or blood phenotype [69], suggesting that the function of MSLN is redundant during normal growth and development. The higher level of MSLN expressed on tumors may help to direct MSLN-targeted therapies more specifically to MSLN+ tumor cells, but given the limited beneficial effects of MSLN targeted therapies observed to this point, perhaps more attention needs to be given to understand the anti-death survival pathways that are upregulated in MSLN+ tumours [70,71]. This may help guide the rational choice of combination therapies that could be used to target MSLN+ tumors in the future.

CONCLUSIONS

Mesothelial cells are dynamic cells important for serosal homeostasis. They are the first line of defense against infectious agents invading the coelomic cavities and play essential roles in the initiation and resolution of inflammation and the immune response. Changes in how mesothelial cells interact with the immune system is likely to be important in the development of serosal diseases such as MM. Determining how the immune system is regulated in both normal serosal

tissues and disease will be crucial to the understanding of the pathophysiology of these diseases and the development of new therapies for MM and non-malignant conditions. This is particularly important in view of the repeated lack of success of many clinical trials where various combinations of immunotherapies and drugs taken off the shelf are trialed without a sound scientific rationale for support.

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Figure Legends

Figure 1. Expression of checkpoint inhibitors by malignant mesothelioma cells can inhibit T cell anti-tumor effector responses. Activation of T cells requires recognition of the specific peptide-MHC (pMHC) antigen complex on the surface of a professional antigen presenting cell (APC) such as a dendritic cell (DC) by the T cell receptor (TCR). The APCs can also express costimulatory molecules CD80/86 ligands which bind with CD28 to deliver a costimulatory signal which in conjunction with a TCR signal can lead to full activation of the T cell. Activated T cells express checkpoint inhibitory molecules such as CTLA-4 and PD-1 to dampen effector responses that bind to CD80/86 and PD-L1 respectively. Signaling via TCR and CTLA-4/PD-1 can lead to inhibition of T cell growth through induction of T cell anergy. CD4+ Tregs can be recruited to the tumor site where they secrete inhibitory cytokines (IL-10 and TGF-β) to suppress T cell responses. Tumor cells can constitutively express the PD-L1 checkpoint inhibitor resulting in anergy of tumor specific T cells and promote tumor growth. Blockade of checkpoint molecules on tumor cells can negate the inhibitory signals delivered to tumor-specific T cells and restore anti-tumor effector immune responses to eliminate the tumor.

Figure 2. CAR-T cell immune therapy to target solid tumors. A. The 3rd and 4th generation CAR-T cells express a short chain variable fragment that has specificity for a tumor-associated antigen such as mesothelin. The scFv chain is linked to a transmembrane domain and an intracellular domain to allow the chimeric receptor to signal and activate the CAR-T cell. The intracellular domain is composed of three different domains consisting of protein modules derived from costimulatory proteins such as OX40/41BB/CD28 and this can help to increase cell survival. **B.** The CD3ζ domain can help facilitate intracellular signaling linked to growth and effector responses such as the secretion of specific cytokines or effector molecules (e.g. perforin and granzyme) that can direct cell lysis of the tumor cell.

Table. Summary of current/recent clinical trials using checkpoint inhibitors, mesothelin-based CAR-T cells for malignant mesothelioma.

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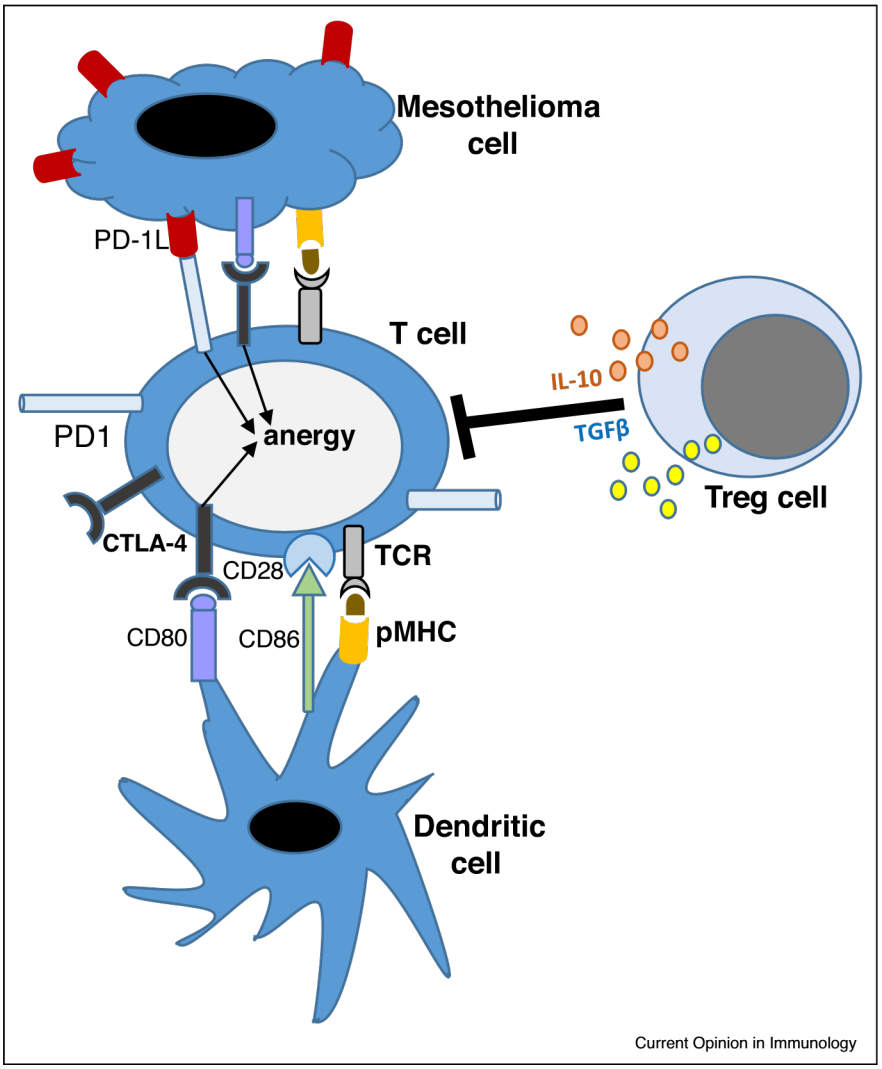
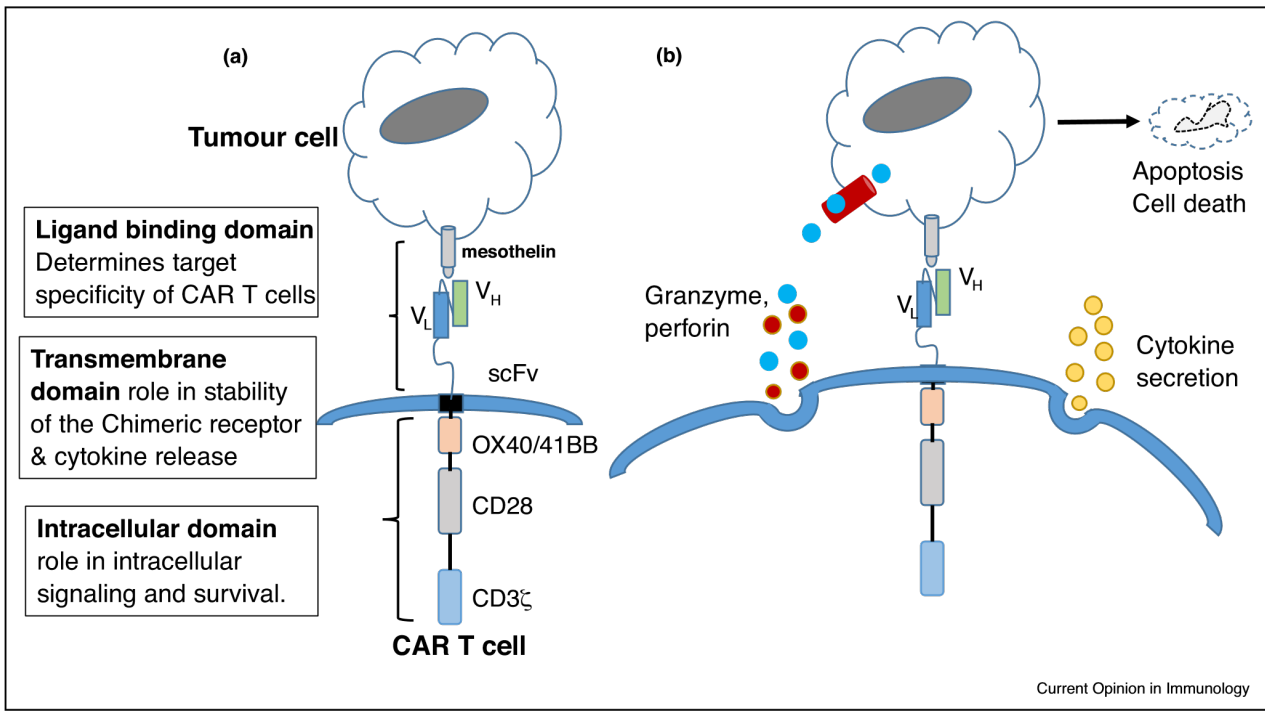
Figure 1



Expression of checkpoint inhibitors by malignant mesothelioma cells can inhibit T cell anti-tumor effector responses. Activation of T cells requires recognition of the specific peptide-MHC (pMHC) antigen complex on the surface of a professional antigen presenting cell (APC) such as a dendritic cell (DC) by the T cell receptor (TCR). The APCs can also express costimulatory molecules CD80/86 ligands which bind with CD28 to deliver a costimulatory signal which in conjunction with a TCR signal can lead to full activation of the T cell. Activated T cells express checkpoint inhibitory molecules such as CTLA-4 and PD-1 to dampen effector responses that bind to CD80/86 and PD-L1 respectively. Signaling via TCR and CTLA-4/PD-1 can lead to inhibition of T cell growth through induction of T cell anergy. CD4+ Tregs can be recruited to the tumor site where they secrete inhibitory cytokines (IL-10 and TGF-b) to suppress T cell responses. Tumor cells can constitutively express the PD-L1 checkpoint inhibitor resulting in anergy of tumor specific T cells and promote tumor growth. Blockade of checkpoint molecules on tumor cells can negate the inhibitory signals delivered to tumor-specific T cells and restore anti-tumor effector immune responses to eliminate the tumor.

Figure 2



CAR-T cell immune therapy to target solid tumors. (a) The 3rd and 4th generation CAR-T cells express a short chain variable fragment that has specificity for a tumor-associated antigen such as mesothelin. The scFv chain is linked to a transmembrane domain and an intracellular domain to allow the chimeric receptor to signal and activate the CAR-T cell. The intracellular domain is composed of three different domains consisting of protein modules derived from costimulatory proteins such as OX40/41BB/CD28 and this can help to increase cell survival. (b) The CD3z domain can help facilitate intracellular signaling linked to growth and effector responses such as the secretion of specific cytokines or effector molecules (e.g. perforin and granzyme) that can direct cell lysis of the tumor cell.

Table 1

Summary of current clinical trials using checkpoint inhibitors, mesothelin-based therapies or CAR T cells/engineered T cells for malignant mesothelioma treatment

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
Clinical trials using checkpoint inhibitors that are not yet recruiting or currently recruiting								
Pembrolizumab in combination with chemotherapy and image-guided surgery for malignant pleural mesothelioma (MPM). NCT03760575	Pembrolizumab Cisplatin Pemetrexed Indocyanine Green (ICG) Image-Guided Surgery	Anti-PD-1 + Chemotherapy + Surgery	Phase 1 trial. Pembrolizumab 200 mg IV every 3 weeks for 2 cycles pre-surgery and 4 cycles post-surgery then every 3 weeks maintenance. Surgery with image guided resection then cisplatin 75 mg/m2 IV and pemetrexed 500 mg/m2 IV every 3 weeks for 4 cycles post-surgery.	20	Pleural mesothelioma	Study related adverse events.	Not yet recruiting	Abramson Cancer Center of the University of Pennsylvania.
Pembrolizumab plus lenvatinib in second line and third line malignant pleural mesothelioma patients (PEMMELA). NCT04287829	Pembrolizumab Lenvatinib	Anti-PD-1 + Multi kinase inhibitor against VEGFR	Phase 2 study. Pembrolizumab 200 mg IV every 3 weeks and lenvatinib 20 mg oral daily in three weekly cycle until disease progression.	36	Pleural mesothelioma.	Objective response rate.	Not yet recruiting	The Netherlands Cancer Institute Merck Sharp and Dohme Corp.
Pembrolizumab + Defactinib in Pleural mesothelioma. NCT04201145	Pembrolizumab Defactinib	Anti-PD-1 + FAK inhibitor	Phase 1 trial. Pembrolizumab IV predetermined dose twice per cycle for 56 days versus pembrolizumab and defactinib oral predetermined dose twice daily for 12 days versus pembrolizumab and defactinib for 35 days. Expansion cohort to follow.	26	Malignant pleural mesothelioma	Maximum Tolerated Duration and pre versus post biomarker activity.	Not yet recruiting	Raphael Bueno, MD Merck Sharp and Dohme Corp.
Pembrolizumab and hypofractionated stereotactic radiotherapy in patients with malignant pleural mesothelioma (MESO-PRIME) NCT04166734	Pembrolizumab Stereotactic Body Radiotherapy (SBRT)	Anti-PD-1 + Radiation	Phase 1 study. Safety and expansion cohorts. Pembrolizumab IV 200 mg every 3 weeks. SBRT at 30 Gy in 3 fractions alternate days in week 3	18	Advanced malignant pleural mesothelioma.	Toxicity rate.	Not yet recruiting.	Royal Marsden NHS Foundation Trust Merck Sharp and Dohme Corp
Nivolumab with chemotherapy in pleural mesothelioma after surgery. NCT04177953	Nivolumab	Anti-PD-1	Phase 2 study. Four cycles (16 weeks) carboplatin AUC5 or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 versus same as above plus 12 cycles (48 weeks) nivolumab (480 mg)	92	Must have undergone cytoreductive surgery with curative intent consisting of extended pleurectomy/ decortication (eP/D) ± hyperthermic intrathoracic chemotherapy.	Progression free survival up to 16 months. Overall survival. Incidence and severity of adverse events	Not yet recruiting	IKF Klinische Krebsforschung GmbH at Krankenhaus Nordwest Bristol-Myers Squibb

Table 1 (*Continued*)

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
Nivolumab and ipilimumab +/− UV1 vaccination as second line treatment in patients with malignant mesothelioma(NIPU). NCT04300244	Nivolumab Ipilimumab UV1 vaccine Leukine	Anti-PD-1 + Anti-CTLA4 +/− UV1 vaccine to increase pool of hTERT specific tumor-reactive T cells	Phase 2 study. Ipilimumab and nivolumab plus UV1 versus ipilimumab and nivolumab.	118	Malignant pleural mesothelioma	Evaluation of efficacy and progression free survival.	Not yet recruiting	Åslaug Helland Oslo University Hospital Ultimovacs ASA Bristol-Myers Squibb
Durvalumab with chemotherapy as first line treatment in advanced pleural mesothelioma (DREAM3R) NCT04334759.	Durvalumab Cisplatin Pemetrexed	Anti-PD-L1 + chemotherapy	Phase 2 study. Durvalumab 1500 mg IV every 3 weeks plus cisplatin 75 mg/ m^2 IV every 3 weeks plus pemetrexed 500 mg/m^2 IV every 3 weeks for 4–6 cycles, followed by maintenance with durvalumab 1500 mg IV every 4 weeks versus standard chemotherapy for 4–6 cycles, followed by observation.	480	Malignant pleural mesothelioma	Overall Survival	Not yet recruiting	PrECOG, LLC. AstraZeneca Australasian Lung Cancer Trials Group University of Sydney
Pembrolizumab plus autologous dendritic cell (DC) vaccine in patients With PD-L1 negative advanced mesothelioma who have failed prior therapies. NCT03546426	Pembrolizumab Dendritic cell vaccine Interleukin 2	Anti-PD-1 + Autologous dendritic cells	Phase 1 study. Pembrolizumab 200 mg IV every 3 weeks. Autologous DCs loaded with autologous tumor homogenate, 10^7 cells intradermal every 3 weeks for up to six doses. IL-2 3 MU subcutaneous from day +2 to day +6 after each DC administration	18	Advanced progressive malignant mesothelioma, PD-L1 Negative	Safety, PD-L1 expression induced by treatment	Not yet recruiting	Istituto Scientifico Romagnolo per lo Studio e la cura dei Tumori
Study of pembrolizumab (MK-3475) in participants with advanced solid tumors (MK-3475-158/ KEYNOTE-158) NCT02628067	Pembrolizumab	Anti-PD-1	Phase 2 study. Pembrolizumab 200 mg IV on Day 1 of each 3-week cycle for up to 35 cycles.	1395	Mesothelioma Anal Squamous Cell carcinoma Biliary adenocarcinoma Neuroendocrine tumors of the lung, appendix, small intestine, colon, rectum, or pancreas Endometrial Carcinoma and others	Objective Response Rate	Recruiting	Merck Sharp and Dohme Corp

Table 1 (Continued)

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
Arginase inhibitor INCB001158 as a single agent and in combination with immune checkpoint therapy in patients with advanced/metastatic solid tumors. NCT02903914	INCB001158 Pembrolizumab	Anti-arginase +/ Anti-PD-1	Phase 1 and 2 study. INCB001158 dose escalation. INCB001158 and pembrolizumab dose escalation.	424	Metastatic Cancer Solid Tumors Colorectal Cancer Gastric Cancer Head and Neck Cancer Melanoma Lung Cancer Renal Cell Carcinoma Bladder Cancer Urothelial Cancer Mesothelioma	Safety and Tolerability and recommendation of phase 2 dose.	Recruiting	Incyte Corporation
Mesothelioma stratified therapy (MiST): A multi-drug phase II trial in malignant mesothelioma. NCT03654833	Rucaparib Abemaciclib Pembrolizumab and bemcentinib Atezolizumab and Bevacizumab	Anti-PARP Anti-CDK Anti-PD-1 Anti-AXL Anti-PD-L1 Anti-VEGF	Phase 2 study. BRCA1/BAP1 negative Rucaparib 600 mg twice daily every 28 days. p16INK4A negative Abemaciclib 200 mg orally twice daily every 28 days. Pembrolizumab 200 mg IV on day 1 every 21 days. Bemcentinib 400 mg on days 1–3 and on day 4 on-wards 200 mg daily every 21-days.	120	Malignant mesothelioma	Disease control rate.	Recruiting	University of Leicester British Lung Foundation Clovis Oncology, Inc. Eli Lilly and Company Merck Sharp and Dohme Corp. BerGenBio ASA Roche Pharma AG University Hospitals, Leicester The Christie NHS Foundation Trust
Study of SO-C101 and SO-C101in combination with pembro in adult patients with advanced/metastatic solid tumors. NCT04234113	SO-C101 Pembrolizumab	Human fusion protein of IL-15. Agonist of the intermediate-affinity IL-2/IL-15Rβγ + Anti-PD-1	Phase 1 study. SO-C101 versus SO-C101 plus pembrolizumab	95	Mesothelioma Renal Cell Carcinoma Non Small Cell Lung Cancer Small-cell Lung Cancer Bladder Cancer Melanoma Merkel Cell Carcinoma Skin Squamous Cell Carcinoma Cervical Cancer Hepatocellular Carcinoma Ovarian Cancer Gastric Cancer And others	Number of patients with dose-limiting toxicities, treatment-emergent adverse events, treatment related adverse events, laboratory test abnormalities, clinically significant change from screening. ECOG performance status.	Recruiting	Solio a.s.

Table 1 (Continued)

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
Study of FAK(defactinib) and PD-1 (pembrolizumab) inhibition in advanced solid malignancies (FAK-PD1) NCT02758587	Defactinib Pembrolizumab	Anti-FAK + Anti-PD-I	Phase 1 and 2 study. Dose escalation pembrolizumab 200 mg IV every 3 weeks plus 200 or 400 mg oral defactinib twice daily.	59	Mesothvlioma Non-small-cell lung carcinoma Pancreatic neoplasms	Adverse events and objective response rate.	Recruiting	NHS Greater Glasgow and Clyde University of Glasgow Cancer Research UK Merck Sharp and Dohme Corp. Verastem, Inc. University of Edinburgh University of Southampton University of Leicester Queen's University, Belfast
Study of MK-4830 as monotherapy and in combination with pembrolizumab (MK-3475) in participants with advanced solid tumors (MK-4830-001) NCT03564691	MK-4830 pembrolizumab	Anti-ILT4 + anti-PD-1	Phase 1 study. Dose escalation and expansion. MK-4830 IV every three weeks for up to 35 cycles. MK-4830 plus pembrolizumab IV every three weeks for up to 35 cycles.	270	Mesothelioma Pancreatic adenocarcinoma	Dose-Limiting Toxicities. Adverse events, objective response rate.	Recruiting	Merck Sharp and Dohme Corp.
Pembrolizumab in patients with advanced malignant pleural mesothelioma. NCT02784171	Pemetrexed Cisplatin Pembrolizumab	Chemotherapy + anti-PD-1	Phase 2/3 study. Pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) every 21 days for 6 cycles versus the same plus pembrolizumab (200 mg) every 21 days for 2 years versus pembrolizumab alone.	126	Histological confirmed malignant mesothelioma. No prior chemotherapy for at least 12 months. No prior immunotherapy or targeted small molecule therapy.	Progression free survival. Overall survival up to 32 months.	Recruiting	Canadian Cancer Trials Group National Cancer Institute, Naples Merck Sharp and Dohme Corp. Intergroupe Francophone de Cancerologie Thoracique University of Southampton
A Study of pembrolizumab in combination with cisplatin and pemetrexed in advanced malignant pleural mesothelioma (MPM) (MK-3475-A17). NCT04153565	Pembrolizumab Cisplatin Pemetrexed	Anti-PD-1 + Chemotherapy	Phase 1 study. Pembrolizumab 200 mg/m2 IV every 3 weeks plus cisplatin 75 mg/m2 IV and pemetrexed 500 mg/m2 IV for 4 - 6 cycles, followed by monotherapy of pembrolizumab up to 35 cycles from first dose.	18	Mesothelioma	Number of participants experiencing dose-limiting toxicity, number of participants with one or more untoward medical occurrences, tolerability.	Recruiting	Merck Sharp and Dohme Corp.

Table 1 (*Continued*)

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
Phase I trial of adjuvant pembrolizumab after radiation therapy for lung-intact malignant pleural mesothelioma. NCT02959463	Pembrolizumab	Radiation + anti-PD-1	Phase 1 study. Hemithoracic radiation followed by pembrolizumab every 3 weeks up to 2 years versus localized palliative radiation over 1–3 weeks followed by pembrolizumab every 3 weeks up to 2 years.	24	Histological confirmed malignant mesothelioma. At least 2 prior cycles of induction chemotherapy.	Adverse side effects. Progression free survival. Overall survival.	Recruiting	M.D. Anderson Cancer Center, National Cancer Institute
Combination of immunotherapy and hyperthermia in advanced malignant mesothelioma. NCT03393858	Pembrolizumab DC-CIK-immunotherapy Hyperthermia	Anti-PD-1 + dendritic cells and cytokine-induced killer (DC-CIK) cells + hyperthermia	Phase 1/2 study. Pembrolizumab (100 mg) every 3 weeks. Two cycles of infused own cultured dendritic cells and cytokine-induced killer (DC-CIK) cells. Hyperthermia twice weekly, maximum 10 times.	40	Histological confirmed malignant mesothelioma. Maximum of one line of platinum-based therapy. Life expectancy >3 months.	Progression free survival up to 24 months. Safety.	Recruiting	Capital Medical University
Trial of pembrolizumab and nintedanib. NCT02856425	Pembrolizumab Nintedanib	Anti-PD-1 + Anti-tyrosine kinase vargeting VEGF and PDGF	Phase 1 study. Nintedanib oral plus pembrolizumab IV	18	Advanced solid tumors including mesothelioma.	Highest dose of a drug or treatment that does not cause unacceptable side effects.	Recruiting	Gustave Roussy, Cancer Campus, Grand Paris
Using a targeted cancer vaccine (Galinpepimut-S) with immunotherapy (Nivolumab) in mesothelioma. NCT04040231	Galinpepimut-S (vaccine) Nivolumab	Vaccine + anti-PD-1	Phase 1 study. Vaccine Galinpepimut-S administered alone on weeks 0 and 2. Nivolumab given over 16 weeks and Sargramostim (CSF-2; 70 mcg) injected subcutaneously on days 0 and 2 of each cycle.	10	Pathologic diagnosis of malignant pleural mesothelioma. Karnofsky performance status >/ – 70% Positive immunohistochemical staining for WT-1. At least one prior course of pemetrexed-based chemotherapy.	Maximum tolerated dose. Followed up to 24 months.	Recruiting	Memorial Sloan Kettering Cancer Center
Checkpoint blockade for inhibition of relapsed mesothelioma. NCT03063450	Nivolumab	Anti-PD-1	Phase 3 study. Nivolumab (240 mg) every 2 weeks for 12 months versus placebo.	336	Histological confirmed malignant mesothelioma. Received at least one prior line of treatment. Life expectancy >3 months.	Progression free survival. Overall survival up to 5 years.	Recruiting	University of Southampton Bristol-Myers Squibb
A study of nivolumab and chemotherapy followed by surgery for mesothelioma. NCT04162015	Nivolumab Pemetrexed Cisplatin or Carboplatin	Anti-PD-1 + Chemotherapy + surgery	Phase 1 study. Two cycles of nivolumab 360 mg, pemetrexed 500 mg/m2 and cisplatin 75 mg/m2 or carboplatin AUC 5 with subsequent pleurectomy/ decortication.	35	Malignant pleural mesothelioma	Number of patients going for surgical resection.	Recruiting	Memorial Sloan Kettering Cancer Center Bristol-Myers Squibb

Table 1 (Continued)

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
Neoadjuvant immune checkpoint blockade in resectable malignant pleural mesothelioma. NCT03918252	Nivolumab Ipilimumab	Anti-PD-1 + Anti-CTLA-4	Phase 1 and 2 study. Preoperative nivolumab 240 mg IV on day -42, -28 and -14. Preoperative nivolumab 3 mg/kg IV on day -42, -28 and Day -14 plus ipilimumab 1 mg/kg IV on day -42.	30	Mesothelioma	Safety profile and feasibility of completing study.	Recruiting	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Bristol-Myers Squibb
A dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of IPI-549. NCT02637531	IPI-549 Nivolumab	Anti- PI3K-gamma + Anti-PD-1	Phase 1 study. Dose escalation IPI-549 orally daily or twice daily until disease progression IPI-549 optimum dose orally with nivolumab 240 mg IV every 2 weeks.	220	Advanced Solid Tumors Non-small Cell Lung Cancer Melanoma Squamous Cell Cancer of the Head and Neck Triple Negative Breast Cancer Adrenocortical Carcinoma Mesothelioma High-circulating Myeloid-derived Suppressor Cells	Dose limiting toxicities. Adverse events and safety laboratory values.	Recruiting	Infinity Pharmaceuticals, Inc.
Nivolumab and ipilimumab in treating patients with rare tumors NCT02834013	Nivolumab Ipilimumab	Anti-PD-1 Anti-CTLA-4	Phase 2 study. Nivolumab IV on days 1, 15, and 29 and ipilimumab IV over on day 1 of 42 day cycle until disease progression versus nivolumab on days 1, 15 and 29.	818	Peritoneal mesothelioma plus 92 other tumors	Overall response rate.	Recruiting	National Cancer Institute.
Phase II nivolumab and ramucirumab for patients with previously treated mesothelioma. NCT03502746	Nivolumab Ramucirumab	Anti-PD-1 + Anti-VEGFR	Phase 2 study. Nivolumab 240 mg IV plus ramucirumab 8 mg/kg IV every 2 weeks for 24 months.	35	Malignant mesothelioma	Response rate.	Recruiting	Arkadiusz Z. Dudek, MD HealthPartners Institute Regions Cancer Care Center Eli Lilly and Company Bristol-Myers Squibb
MTG201 plus nivolumab in patients with relapsed pleural mesothelioma. NCT04013334	MTG201 Nivolumab	Gene therapy for REIC/Dkk -3 gene + Anti-PD-1	Phase 2 study. MTG201 intratumoral on days 1, 8, 22 and 50. Nivolumab 480 mg IV every 4 weeks.	12	Malignant pleural mesothelioma	Objective response rate.	Recruiting	Momotaro-Gene Inc. Baylor College of Medicine Synteract, Inc.

Table 1 (Continued)

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
Phase 1/2 study exploring the safety, tolerability, and efficacy of INCAGN01876 combined with immune therapies in advanced or metastatic malignancies. NCT03126110	INCAGN01876 Nivolumab Ipilimumab	GITR agonist + Anti-PD-1 + Anti-CTLA-4	Phase 1 and 2 study. INCAGN01876 IV plus nivolumab IV versus INCAGN01876 IV plus ipilimumab IV versus INCAGN01876 IV plus nivolumab IV plus ipilimumab IV.	285	Advanced malignancies Metastatic cancer	Safety and tolerability and objective response rate.	Recruiting	Incyte Biosciences International Sàrl
Stereotactic body radiation therapy and avelumab immunotherapy for treatment of malignant mesothelioma. NCT03399552	Stereotactic body radiation Avelumab	Radiation + Anti-PD-L1	Phase 1 and 2 study. Avelumab 10 mg/kg IV every other week and short course of SBRT after the first two doses of avelumab.	27	Malignant mesothelioma	Overall response rate.	Recruiting	Memorial Sloan Kettering Cancer Center Pfizer
Naptumomab estafenatox in combination with durvalumab in subjects with selected advanced or metastatic solid tumors. NCT03883854	Naptumomab estafenatox Durvalumab	Anti-5T4 tumor antigen + Anti-PD-L1	Phase 1 study. Dose escalation and expansion study. Naptumomab estafenatox treatment on first four days of each 21-day cycle, at 2, 5, 10, 15 or 20 µg/kg IV. Durvalumab given 1120 mg day 1 of 21 day cycle. Expansion Naptumomab estafenatox with durvalumab at for 3 or more cycles depending on PK results.	45	Mesothelioma Breast Cancer Epithelial Ovarian Cancer Cervical Cancer Pancreatic Cancer Endometrial Cancer Renal Cancer Urothelial Cancer Head and Neck Cancer Melanoma Hepatic Carcinoma Prostate Cancer NSCLC	The incidence and characteristics of adverse events. The highest dose that does not cause unacceptable side effects. Establish recommended phase 2 dose.	Recruiting	NeoTX Therapeutics Ltd. AstraZeneca Pharmaceuticals PLC
Atezolizumab, pemetrexed, disodium cisplatin and Surgery with or without radiation therapy in treating patients with stage I–III pleural malignant mesothelioma. NCT03228537	Cisplatin Pemetrexed Atezolizumab	Surgery + radiation + chemotherapy + anti-PD-L1	Phase 1 study. Pemetrexed and cisplatin every 21 days for 4 cycles followed by extrapleural pneumonectomy (EPP) or pleural decortication. Patients who undergo EPP will then get radiation therapy. This is followed by atezolizumab every 21 days for up to 12 months.	28	Epithelioid or biphasic malignant mesothelioma. No prior malignancy.	Progression free survival. Overall survival.	Recruiting	National Cancer Institute

Table 1 (Continued)

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
BEAT-meso: Bevacizumab and atezolizumab in malignant pleural mesothelioma. NCT03762018	Bevacizumab Atezolizumab Carboplatin Pemetrexed	Anti-VEGFA + Anti-PD-L1 + chemotherapy	Phase 3 study. Bevacizumab 15 mg/kg IV every 3 weeks plus 4–6 cycles carboplatin AUC 5 plus pemetrexed 500 mg/m^2 IV every 3 weeks versus atezolizumab 1200 mg IV every 3 weeks plus bevacizumab 15 mg/kg IV every 3 weeks plus 4–6 cycles of carboplatin AUC 5 plus pemetrexed 500 mg/m^2. intravenously on day 1 every 3 weeks.	320	Advanced malignant pleural mesothelioma	Progression free survival and overall survival.	Recruiting	European Thoracic Oncology Platform Hoffmann-La Roche
Clinical trials using checkpoint inhibitors that are active but not recruiting or unknown								
Pembrolizumab immunotherapy versus standard chemotherapy for advanced pre-treated malignant pleural mesothelioma. NCT02991482	Pembrolizumab Gemcitabine or vinorelbine	Anti-PD-1 versus chemotherapy	Multicentre randomised phase 3 study. Pembrolizumab (200 mg) every 3 weeks for 2 years versus gemcitabine (1000 mg/m^2) or vinorelbine (30 mg/m^2, or p.o 60/80 mg/m^2) on days 1 and 8 of every 3-week cycle.	144	Histological confirmed malignant mesothelioma, Progressing after or on previous platinum-based chemotherapy. Life expectancy >3 months.	Objective tumor response up to 24 months. Safety.	Active not recruiting	European Thoracic Oncology Platform Merck Sharp and Dohme Corp. Frontier Science Foundation, Hellas
Ipilimumab and nivolumab in the treatment of malignant pleural mesothelioma (INITIATE). NCT03048474	Ipilimumab Nivolumab	Anti-CTLA-4 + Anti-PD-1	Phase 2 study. Nivolumab 240 mg every 2 weeks for 2 years plus ipilimumab 1 mg/Kg on week 1, 7, 13 and 19.	36	Malignant pleural mesothelioma	Disease control rate.	Active, not recruiting	The Netherlands Cancer Institute Bristol-Myers Squibb
Study of nivolumab combined with ipilimumab versus pemetrexed and cisplatin or carboplatin as first line therapy in unresectable pleural mesothelioma patients. NCT02899299	Nivolumab Ipilimumab Pemetrexed Cisplatin or carboplatin	Anti-PD-1 + Anti-CTLA-4 versus Chemotherapy	Phase 3 study. Nivolumab and Ipilimumab. Specified dose on specified days. Compared with pemetrexed and cisplatin (or carboplatin). Specified dose on specified days.	605	Malignant pleural mesothelioma	Overall survival.	Active, not recruiting	Bristol-Myers Squibb Ono Pharmaceutical Co. Ltd
MED14736 or MED14736 + tremelimumab in surgically resectable malignant pleural mesothelioma. NCT02592551	MED14736 (Durvalumab) Tremelimumab	Anti-PD-L1 + Anti-CTLA-4	Phase 2 study. MED14736 15 mg/kg IV once, one to six weeks before surgical resection versus MED14736 1500 mg IV once plus tremelimumab 75 mg IV once, one to six weeks before surgical resection.	20	Malignant pleural mesothelioma	Intratumoral CD8/ Treg ratio. % of ICOS + CD4 T cells. Tumor expression of PD-L1.	Active not recruiting	Baylor College of Medicine

Table 1 (Continued)

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
Diadem to investigate the activity and safety of durvalumab (Diadem) NCT04115111	Durvalumab	Anti-PD-L1	Phase 2 study. Durvalumab IV every 4 weeks until disease progression.	57	Pleural mesothelioma	Proportion of survived patients at 16 weeks and free from progression.	Active not recruiting	Mario Negri Institute for Pharmacological Research
Phase II MEDI4736 in combination with chemotherapy for first-line treatment of unresectable mesothelioma. NCT02899195	Durvalumab Pemetrexed Cisplatin	Anti-PD-L1 + chemotherapy	Phase 2 study. Durvalumab 1120 mg IV on Day 1 of 21 day cycle followed by pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 IV.	55	Mesothelioma	Overall survival.	Active, not recruiting	PrECOG, LLC, AstraZeneca
Nivolumab monotherapy or nivolumab plus ipilimumab for unresectable malignant pleural mesothelioma (MPM) patients. NCT02716272	Nivolumab Ipilimumab	Anti-PD-1 + anti-CTLA-4	Phase 2 study. Nivolumab (3 mg/kg) every 2 weeks versus above plus ipilimumab (1 mg/kg) every 6 weeks.	125	Histological confirmed malignant mesothelioma. Available tumor samples for measuring PD-L1. <10% weight loss in last 3 months. Life expectancy >3 months No prior immunotherapy.	Disease control rate. Progression free survival. Overall survival. Adverse events. Quality of life.	Active, not recruiting	Intergroupe Francophone de Cancerologie Thoracique
A study of CA-170 (oral PD-L1, PD-L2 and VISTA checkpoint antagonist) in patients with advanced tumors and lymphomas. NCT02812875	CA-170	Anti-PD-L1, PD-L2 and VISTA	Phase 1 study. Orally once or twice daily. Dose escalation (Phase 1a) and dose expansion (Phase 1b) in patients with tumors responsive to anti-PD-1 or anti-PD-L1 inhibitors and/or in tumor types known to express PD-L1 or VISTA.	300	Advanced Solid Tumors or Lymphomas including mesothelioma.	Number of patients with dose-limiting toxicity in first treatment cycle. Maximum tolerated dose of CA-170. Recommended Phase 2 dose of CA-170.	Active, not recruiting	Curis, Inc.
A clinical study with tremelimumab as monotherapy in malignant mesothelioma. NCT01649024	Tremelimumab	Anti-CTLA-4	A second-line, single arm, phase 2 study. Tremelimumab (15 mg/kg) on day 1 every 12 weeks for 4 doses.	29	Histological confirmed malignant mesothelioma. Maximum of one line of platinum-based therapy Life expectancy >3 months.	Objective tumor response up to 24 weeks. Safety.	Unknown	Azienda Ospedaliera Universitaria Senese
A pilot window-of-opportunity study of the anti-PD-1 antibody pembrolizumab in patients with resectable malignant pleural mesothelioma NCT02707666	Pembrolizumab Surgery Cisplatin Pemetrexed	Anti-PD-1 + surgery + chemotherapy	Phase 1 study. Neoadjuvant pembrolizumab followed by surgery, followed by adjuvant pemetrexed and cisplatin	15	Malignant pleural mesothelioma	Gamma-Interferon Gene Expression profile (GEP) response rate, number of participants with adverse events	Unknown	University of Chicago

Table 1 (*Continued*)

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
Pembrolizumab in treating patients with malignant mesothelioma. NCT02399371	Pembrolizumab	Anti-PD-1	Phase 2 study. Pembrolizumab IV every 21 days for up to 24 months in the absence of disease progression.	65	Malignant pleural or peritoneal mesothelioma, biphasic, epithelioid, sarcomatoid or recurrent mesothelioma.	Ability of PD-L1 to predict response, Overall survival, progression free survival, disease control rate.	Unknown	University of Chicago
A study of tremelimumab combined with the anti-PD-L1 MEDI4736 antibody in malignant mesothelioma (NIBIT-MESO-1). NCT02588131	Tremelimumab MEDI4736 (durvalumab)	Anti-CTLA-4 + anti-PD-L1	Phase 2 study. Tremelimumab (1 mg/kg) plus MEDI 4736 (20 mg/kg) every four weeks for 4 doses, then MEDI4736 (20 mg/kg) every four weeks for additional 9 doses.	40	Histological confirmed malignant mesothelioma. Available tumor samples. Maximum of one line of platinum-based therapy. Measurable disease. Life expectancy >3 months.	Objective response rate. Disease control rate. Progression free survival. Overall survival. Adverse events.	Unknown	Italian Network for Tumor Biotherapy Foundation AstraZeneca
Clinical trials using other immunotherapy-based treatments, including vaccines, that are recruiting or active but not recruiting								
Efficacy and safety of rAd-IFN administered with celecoxib and gemcitabine in patients with malignant pleural mesothelioma (INFINITE). NCT03710876	rAd-IFN celecoxib gemcitabine	Adenovirus type 5 (Ad5)-vector encoding interferon alpha-2b (IFNa2b) gene + Nonsteroidal anti-inflammatory + Chemotherapy	Phase 3 study. rAd-IFN day 1 plus celecoxib 400 mg oral twice daily up to day 14 plus gemcitabine 1250 mg/m2 on days 14 and 21 [i.e. days 1 and 8 of the first gemcitabine treatment cycle], repeated every 3 weeks until disease progression versus celecoxib plus gemcitabine.	300	Malignant pleural mesothelioma	Overall survival.	Recruiting	Trizell Ltd University of Pennsylvania
Phase II study of adjuvant WT-1 analog peptide vaccine in MPM patients after MSK10-134. NCT01890980	WT-1-vaccine Montanide GM-CSF	Vaccine Adjuvant Immune stimulant	Phase 2 study. WT-1-vaccine Montanide on weeks 0, 2, 4, 6, 8, and 10. Sargramostim (GM-CSF) (70 mcg) SC On days 0 and 2 of each vaccination versus montanide and GM-CSF.	60	Malignant pleural mesothelioma	1-Year progression free survival.	Active, not recruiting	M.D. Anderson Cancer Center U.S. Army Medical Research and Development Command Memorial Sloan Kettering Cancer Center Sellas Life Sciences Group
Clinical trials that are anti-mesothelin-based								
Pembrolizumab with or without anetumab ravtansine in treating patients with mesothelin-positive pleural mesothelioma. NCT03126630	Pembrolizumab Anetumab ravtansine	Anti-PD-1 + Anti-MSLN antibody conjugated to maytansinoid tubulin inhibitor DM4.	Phase 1 and 2 study. Pembrolizumab versus pembrolizumab IV plus anetumab ravtansine IV repeated every 21 days for up to 2 years.	134	Mesothelin positive pleural mesothelioma.	Recommended phase 2 dose of anetumab ravtansine with combination of pembrolizumab and objective response rate.	Recruiting	National Cancer Institute

Table 1 (Continued)

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
Anti-mesothelin immunotoxin LMB-100 followed by pembrolizumab in malignant mesothelioma. NCT03644550	LMB-100 Pembrolizumab	Anti-mesothelin immunotoxin + anti-PD-1	Phase 2 study. LMB-100 on days 1, 3 and 5 of two 21-day cycles. Pembrolizumab every 21 days starting with cycle 3, for up to 2 years.	38	Histological confirmed epithelioid or biphasic malignant mesothelioma. Available tumor samples. At least one line of platinum-based therapy. Measurable disease.	Objective response rate.	Recruiting	National Cancer Institute
Mesothelin-targeted immunotoxin LMB-100 in combination with tofacitinib in persons with previously treated pancreatic adenocarcinoma, cholangiocarcinoma and other mesothelin expressing solid tumors. NCT04034238	LMB-100 Tofacitinib	Anti-mesothelin immunotoxin + JAK1/3 inhibitor	Phase 1 study. LMB-100 dose escalation and expansion plus tofacitinib. LMB-100 IV on days 4, 6 and 8 of 21 day cycle and tofacitinib orally twice daily on days 1 – 10 of each cycle until disease progression.	45	Epithelioid Mesothelioma cholangiocarcinoma, extrahepatic pancreatic adenocarcinoma	Safety and tolerability of LMB-100 with tofacitinib. Timing of anti-LMB-100 anti- drug antibody development.	Recruiting	National Cancer Institute
First-in-human study of BAY2287411 injection, a thorium-227 labeled antibody-chelator conjugate, in patients with tumors known to express mesothelin. NCT03507452	BAY2287411	Thorium-227 labeled MSLN antibody-chelator conjugate	Phase 1 study. Dose escalation. Single dose Thorium-227 1.5 MBq on day 1 of 6 week cycle. Increase in steps of 1.0 or 1.5 MBq with total antibody dose range of 10 – 50 mg. Dose expansion to be determined based on risk/ benefit.	228	Advanced recurrent epithelioid mesothelioma, serous ovarian cancer, metastatic or locally advanced pancreatic ductal adenocarcinoma.	Incidence of dose-limiting toxicity. The incidence of treatment-emergent adverse events.	Recruiting	Bayer
Study of HPN536 in patients with advanced cancers associated with mesothelin expression NCT03872206	HPN536	MSLN antibody conjugated drug undefined.	Phase 1/2a study. Part 1 dose escalation. HPN536 once weekly until estimated therapeutic dose is reached. Part 2 dose expansion. HPN536 once weekly at recommended dose.	87	Phase 1. Epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, or pancreatic adenocarcinoma. Phase 2. As above and mesothelioma.	Phase 1. Assess initial safety and determination of recommended phase 2 dose. Phase 2 overall response rate.	Recruiting	Harpoon Therapeutics
A Clinical study of anetumab ravtansine in adults with solid tumors who have been treated in previous bayer-sponsored anetumab ravtansine studies. NCT03926143	Anetumab ravtansine	Anti-MSLN antibody conjugated to maytansinoid tubulin inhibitor DM4.	Phase 2 study. Anetumab-ravtansine IV as for parent study.	20	Adult patients with solid cancer (and mesothelioma) who received anetumab-ravtansine treatment in a completed Bayer study.	Incidence of treatment-emergent adverse events.	Enrolling by invitation	Bayer

Table 1 (*Continued*)

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
Mesothelin-targeted immunotoxin LMB-100 in people with malignant mesothelioma NCT02798536	LMB-100 Nabpaditaxel	Anti-mesothelin immunotoxin + tubulin inhibitor	Phase 1 study. LMB-100 dose escalation and expansion. IV on days 1, 3 and 5 of 21 day cycle up to 4 cycles. LMB-100+ nab-paclitaxel dose escalation and expansion. LM-100 as above nab-paditaxel IV on days 1 and 8 of 21 day cycle up to 6 cycles.	21	Epithelioid or biphasic Mesothelioma	Determine recommended phase 2 dose of LMB-100 and determine objective response rate.	Active, not recruiting	National Cancer Institute
Clinical trials using CAR T cells and other engineered T cells								
Malignant pleural disease treated with autologous T cells genetically engineered to target the cancer-cell surface antigen mesothelin. NCT02414269	CAR T cells (iCasp9M28z T cells) Cyclophosphamide	Immune activation + CAR T cells (target mesothelin on tumor cells)	Phase 1 study. Transfusion of iCasp9M28z T cells with or without prior cyclophosphamide (1.5 g/m^2), 2 7 days before T cell infusion.	66	Radiology confirmed malignant pleural disease. For malignant pleural mesothelioma, previously treated with at least one treatment regimen. >10% of tumor cells express mesothelin	Composite measure of severity and number of adverse events. Changes in levels of serum mesothelin related peptide.	Recruiting	Memorial Sloan Kettering Cancer Center
CAR T cells in mesothelin expressing cancers NCT03054298	CAR T cells (huCART-MESO) Cyclophosphamide	Immune activation + CAR T cells (target mesothelin on tumor cells)	Phase 1 study. Single dose of 1 3 x 10^7/m^2 lentiviral transduced huCART-meso cells IV or IPI plus or minus cyclophosphamide.	30	Pleural mesothelioma Peritoneal mesothelioma Lung Adenocarcinoma Ovarian Cancer Peritoneal Carcinoma Fallopian Tube Cancer	Number of participants with treatment-related adverse events.	Recruiting	University of Pennsylvania Stand Up To Cancer Lustgarten
Autologous CAR-T/TCR-T cell immunotherapy for malignancies NCT03638206	CAR-T/TCR-T cells	Target different for different tumors. For mesothelioma, anti-Mesothelin antibody.	Phase 1 and 2 study. CAR-T cell immunotherapy with different specific chimeric antigen receptors for different tumor types.	73	Mesothelioma B-cell acute lymphoblastic leukemia Lymphoma Myeloid leukemia Multiple myeloma Hepatoma and others	Number of participants with adverse events	Recruiting	Shenzhen BinDeBio Ltd. The First Affiliated Hospital of Zhengzhou University
Phase 1/2 trial of TC-210 T cells in patients with advanced mesothelin-expressing cancer. NCT03907852	TC-210 T	T cells with anti-mesothelin	Phase 1 and 2 study. TC-210 T or lymphodepletion followed by TC-210 T. NSCLC patients will receive TC-210 or TC-210 followed by anti-PD-1.	70	Mesothelioma Cholangiocarcinoma Ovarian cancer Non small cell lung cancer	Establish the recommended Phase 2 dose. evaluate the efficacy of autologous genetically modified TC-210 T cells	Recruiting	TCR2 Therapeutics

Table 1 (Continued)

Trial/acronym ClinicalTrials.gov identifier	Study medication/ biological	Mechanism	Study design	Patients (n)	Inclusion criteria+	Primary outcome measures	Recruitment status	Sponsors and collaborators
Intraperitoneal MCY-M11 (mesothelin-targeting CAR) for treatment of advanced ovarian cancer and peritoneal mesothelioma. NCT03608618	MCY-M11	Mesothelin-specific CAR	Phase 1 study. Dose escalation MCY-M11 IP once weekly for 3 weeks.	15	Peritoneal mesothelioma Fallopian Tube adenocarcinoma Adenocarcinoma of the ovary Primary peritoneal carcinoma.	Incidence and severity of adverse events	Recruiting	MaxCyte, Inc. CTI Clinical Trial and Consulting Services
Genetically modified T cells in treating patients with stage IIIB/IV non-small cell lung cancer or mesothelioma. NCT02408016	Aldesleukin Autologous WT1-TCRc4 Gene-transduced CD8-positive Tcm/Tn lymphocytes Cyclophosphamide	Aldesleukin (Recombinant IL-2) + cyclophosphamide (stimulate immune system) + transduced CD8+ cells (target WT1+ tumor cells)	Phase 1 study. Autologous WT1-TCRc4 gene-transduced CD8-positive Tcm/Tn lymphocytes on days 0 and 14, cyclophosphamide on days 11 and 12 and aldesleukin twice a day for 14 days. Phase 2 study. Autologous WT1-TCRc4 gene-transduced CD8-positive Tcm/Tn lymphocytes after cyclophosphamide and aldesleukin twice daily for 14 days. Patients then undergo surgery 3–4 weeks after T cell infusion.	20	For mesothelioma, histological confirmed malignant mesothelioma. Tumors must express human leukocyte antigen (HLA)-A*0201 and WT1. Must have received at least one line of therapy or declined therapy.	Evidence and nature of toxicity. Generation of naive T cell and central memory T cell subsets. Persistence of transduced T cells. Functional capacity of transferred cells. Time to progression.	Active, not recruiting	Fred Hutchinson Cancer Research Center National Cancer Institute
Treatment of relapsed and/or chemotherapy refractory advanced malignancies by CART-meso. NCT02580747	CAR T cells	Anti-meso-CAR vector transduced T cells	Phase 1 study. Dose escalation anti-meso-CAR retroviral vector-transduced autologous-derived T cells on days 0, 1, 2 in the absence of disease progression or unacceptable toxicity.	20	Malignant mesothelioma Pancreatic cancer Ovarian Tumor Triple negative breast cancer Endometrial cancer Other mesothelin positive tumors	Study related adverse events.	Unknown	Chinese PLA General Hospital

These studies are as published on ClinicalTrials.gov at the time of manuscript preparation.