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Malignant Mesothelioma: Advances in Immune Checkpoint Inhibitor and Mesothelin Targeted Therapies

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Abstract

Malignant mesothelioma is an aggressive cancer with poor prognosis and limited treatment options. For many years the only FDA approved first-line treatment for unresectable mesothelioma was pemetrexed plus cisplatin. However, the recent approval of nivolumab plus ipilimumab for frontline treatment of patients with pleural mesothelioma marks a significant milestone for the treatment of this disease. This review describes the recent advances in therapeutic strategies for treatment of patients with advanced unresectable mesothelioma. We highlight the emerging use of immunotherapy and mesothelin-targeted therapies for the management of malignant mesothelioma.

Keywords

mesothelioma; immunotherapy; PD-1/PD-L1 inhibitor; CTLA-4 inhibitor; mesothelin; CAR-T cells

INTRODUCTION

Malignant mesothelioma is an uncommon malignancy that arises from the mesothelial cells lining the pleura, peritoneum, pericardium and tunica vaginalis. About 3300 new cases are diagnosed in the United States annually.[1] It has an aggressive clinical course, with approximately 2500 deaths annually and estimated five year survival rates of 10%.[2-4] The three main histologic subtypes of malignant mesothelioma are epithelioid, biphasic, and sarcomatoid, with median survival of 19, 12, and 4 months for pleural mesothelioma respectively.[5] The overall five year survival is significantly better for patients with peritoneal mesothelioma and these patients tend to have predominantly epithelioid histology.[6]

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Risk factors for malignant mesothelioma include asbestos exposure, prior radiation therapies, and genetic factors. Malignant mesothelioma is predominantly seen in individuals with prior asbestos exposure, with a long latent period between exposure and disease development.[7] However, only a small number of individuals exposed to asbestos will ultimately develop mesothelioma.[7] Cancer survivors who have received prior radiation for treatment of Hodgkin lymphoma, breast cancer, and testicular cancer are also at higher risk of developing mesothelioma.[8-11] Several recent studies have also shown that individuals with germline *BRCA1 associated protein-1* (*BAP1*) mutations are at an increased risk of developing mesotheliomas. These patients have earlier onset of disease as well as longer overall survival compared to those without germline *BAP1* mutations and are at increased risk of developing other cancers including uveal melanomas, cutaneous melanomas and renal cell carcinoma.[12-18]

Although mesothelioma is a rare cancer, many phase 1, 2, and multicenter, randomized phase 3 clinical trials have been conducted over the past several years.[19] Despite these efforts, no drug had received United States (US) FDA approval for this disease since the approval of pemetrexed in combination with cisplatin in 2004.[20, 21] However, on October 2, 2020 the FDA approved nivolumab plus ipilimumab as initial therapy for patients with advanced pleural mesothelioma. Given the significant advances in understanding the biology of mesothelioma and development of new therapeutics, it is likely more agents could receive regulatory approval in the near future. Several recent reviews have described in detail different agents in clinical trials for treatment of mesothelioma.[22, 23] This review will focus primarily on immune checkpoint inhibitors and mesothelin targeted therapies.

CHEMOTHERAPY FOR MALIGNANT MESOTHELIOMA

Numerous trials have investigated first line chemotherapy options for mesothelioma.[24-28] A seminal 2003 randomized phase 3 trial that enrolled 456 patients found that the combination of pemetrexed and cisplatin compared to cisplatin alone improved median OS (12.1 months vs 9.3 months), median progression free survival (PFS) (5.7 months vs 3.9 months), and response rates (41.3% vs 16.7%).[21] In select patients, the addition of bevacizumab to chemotherapy may also be considered. In the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS), a randomized, open-label phase 3 clinical trial, 448 patients with pleural mesothelioma were treated with pemetrexed plus cisplatin with or without bevacizumab 15 mg/kg in 21 day cycles.[29] Median OS and PFS were 18.8 months and 9.2 months with the addition of bevacizumab versus 16.1 months and 7.3 months without it. The addition of bevacizumab also resulted in a higher percentage of patients with Grade 3 or higher hypertension (25% vs 0%) and thrombosis (6% vs 1%). To date, platinum therapy with pemetrexed and vitamin supplementation is the mainstay of treatment for surgically unresectable mesothelioma.[21, 30] There are currently no FDA approved therapies for second line treatment of mesothelioma in the US.

IMMUNOTHERAPY WITH IMMUNE CHECKPOINT INHIBITORS AS NEW FRONTLINE THERAPY OPTION

The field of immuno-oncology has rapidly grown in the past decade with the increasing use of immune checkpoint inhibitors (ICIs) for a number of malignancies. The two main pathways targeted by current ICIs are the CTLA-4/B7 and PD-1/PD-L1 axes, which play critical regulatory roles in attenuating T cell activation physiologically.[31] Tumors often coopt these pathways to evade immune destruction. By blocking these inhibitory signals of T cell activation, ICIs reinvigorate T cells to kill tumor cells.

Examples of ICIs used in the clinic include the CTLA-4 inhibitors ipilimumab and tremelimumab, the PD-1 inhibitors nivolumab and pembrolizumab, and the PD-L1 inhibitors durvalumab, avelumab, and atezolizumab. These ICIs have been investigated in a number of clinical trials for advanced mesothelioma as monotherapy (Table 1) and in combination therapies (Tables 2 and 3). On October 2, 2020, the US FDA approved the combination of nivolumab plus ipilimumab as first line treatment for patients with unresectable malignant pleural mesothelioma.

CTLA-4 inhibitor monotherapy

Based on small phase 2 studies of tremelimumab, which showed anti-tumor responses in some patients,[32, 33] a large randomized, double-blind, phase 2b study (DETERMINE) assigned 571 patients with relapsed pleural and peritoneal mesothelioma to either tremelimumab 10 mg/kg or placebo every 4 weeks for 7 doses and every 12 weeks thereafter.[34] The trial found no statistically significant difference in the primary endpoint of OS between the two groups, with median OS of 7.7 months and 7.3 months in the tremelimumab and placebo group respectively, hazard ratio 0.92 [95% CI 0.76-1.12], p=0·41. Grade 3 adverse events occurred more frequently in the tremelimumab group (65%) compared to the placebo group (48%), with the most common being diarrhea. Based on these results, single agent tremelimumab is not indicated for 2nd or 3rd therapy in mesothelioma.

PD-1 and PD-L1 blocking antibody monotherapy

Pembrolizumab has been investigated as a single agent for pretreated patients with mesothelioma. KEYNOTE-028 was a single-arm phase 1b multicohort basket trial that treated patients with PD-L1 positive (defined as ≥1% expression in the tumor cells) tumors. Twenty-five patients with pleural mesothelioma who had failed or were unable to receive standard therapy, received pembrolizumab 10 mg/kg every 2 weeks up to 2 years or progression or intolerable toxicity. Primary endpoints were safety and tolerability and objective response rate (ORR). Five patients (20%) had objective tumor response and 13 (52%) had stable disease.[35] Importantly, the responses were durable with a median duration of response of 12 months.

While KEYNOTE-028 demonstrated the efficacy of pembrolizumab in patients selected for PD-L1 positive mesothelioma, the University of Chicago evaluated the efficacy of pembrolizumab in PD-L1 unselected patients with mesothelioma. In this single-arm phase 2

trial, 64 patients with peritoneal and pleural mesothelioma who had progressed on platinum therapy were enrolled.[36] Pembrolizumab 200 mg was administered every 21 days with primary endpoints to determine objective response rate and to assess the optimal PD-L1 cutoff. ORR of 19%, median PFS of 4.5 months, and median OS of 11.5 months were reported. There was a trend toward a longer PFS in PD-L1 expressing patients. There was a significantly higher RR with high vs. no PD-L1 expression (43% vs. 7%, p=0.01). When used as a continuous marker, higher PD-L1 expression was associated with a higher response rate (ROC area 0.69). No optimal PD-L1 threshold was established.

The phase 3 PROMISE-meso trial randomized 144 patients with advanced pre-treated mesothelioma to pembrolizumab 200 mg every three weeks or physician's choice of salvage chemotherapy.[37] The ORR was 22% for pembrolizumab compared to 6% with chemotherapy. However, study results did not show a statistically significant improvement in median PFS or in median OS. Median PFS was 2.5 months in the pembrolizumab group vs 3.4 months in the chemotherapy group (HR 1.06; 95% CI, 0.73-1.53, p=0.76). Median OS was 10.7 months in the pembrolizumab arm and 12.4 months in the chemotherapy arm (HR=1.12; 95% CI, 0.74-1.69; p=0.59).

Studies using anti-PD-1 nivolumab monotherapy in recurrent advanced mesothelioma have been reported from studies conducted in the Netherlands, Japan, and the United Kingdom. The Dutch study NivoMes was a single-center, single arm, phase 2 study of 34 patients with recurrent pleural mesothelioma who received nivolumab 3 mg/kg every two weeks.[38] The primary endpoint was disease control rate assessed at 12 weeks. Study investigators reported an ORR of 24%, median PFS of 2.6 months, and median OS of 11.8 months. The overall disease control rate was 47%. Half of the patients with stable disease (n=4), achieved disease stability for greater than 6 months. The safety profile included one treatment-related death from pneumonitis. Responses by PD-L1 status on baseline and on-study biopsies showed that even patients with negative PD-L1 expression derived clinical benefit (defined as patients with PR, CR, and prolonged SD ≥ 6 months). Overall, PD-L1 expression on baseline or on-study biopsies did not correlate with outcome (p=0.43 and 0.66, respectively).

MERIT was an open label, single arm, Japanese phase 2 study of nivolumab for patients with advanced pleural mesothelioma resistant to ≤2 regimens of chemotherapy.[39] Thirty-four patients received nivolumab 240 mg every two weeks with a reported ORR of 29%, median PFS of 6.1 months, and median OS of 17.3 months. Based on the results of the MERIT study, nivolumab was approved in August 2018 by the Japan's Ministry of Health, Labour and Welfare for unresectable advanced or recurrent malignant pleural mesothelioma which had progressed after chemotherapy.[40] CONFIRM is an ongoing phase 3 (NCT03063450), randomized, placebo-controlled United Kingdom trial that is currently recruiting up to 336 patients with pleural or peritoneal mesothelioma who have received at least two lines of prior therapy to receive either nivolumab monotherapy or placebo.[41] The primary efficacy endpoint will be overall survival and study completion is expected to be in 2021.

Hassan et al from the National Cancer Institute, Bethesda conducted a phase 2 study of avelumab, an anti-PD-L1 antibody, in patients with unresectable mesothelioma that progressed after platinum and pemetrexed treatment, (JAVELIN).[42] The primary efficacy

endpoints were objective response rates and PFS. Fifty-three patients were given avelumab, 10 mg/kg every 2 weeks. ORR was 9% (1 complete response, 4 partial responses, 26 stable disease) with median PFS of 4.1 months and median OS of 10.7 months. The responses and PFS differed based on PD-L1 positivity. ORR was 14.3% in PD-L1 positive (≥5% cutoff) patients vs 8.0% in PD-L1 negative (<5% cutoff) patients, and median PFS was 17.1 weeks in PD-L1 positive vs 7.4 weeks in PD-L1 negative patients.

In summary, these phase 2 studies of anti-PD-1 or anti-PDL1 immune checkpoint inhibitors demonstrated some efficacy in patients previously treated with chemotherapy. These studies formed the basis of combination studies of immune checkpoints inhibitors in this disease as well as evaluating them in the front-line setting.

Anti-CTLA-4 plus Anti-PD-1/PDL-1 Combination Studies for Previously Treated Patients

Tremelimumab in combination with durvalumab was examined in the open-label, single-arm, phase 2 NIBIT-MESO-1 trial.[43] Forty patients with unresectable pleural or peritoneal mesothelioma received tremelimumab 1 mg/kg and durvalumab 20 mg/kg every 4 weeks for 4 doses, followed by maintenance durvalumab. The primary endpoint was ORR which was observed to be 28%, with a median PFS of 5.7 months and median OS of 16.6 months. The median duration of response was impressive at 16.6 months. Tumor PD-L1 expression did not correlate with the response or survival outcomes. 18% of the patients had grade 3-4 treatment-related adverse events (AEs) with no treatment related deaths.

Other studies have evaluated combining nivolumab with ipilimumab for recurrent malignant pleural mesothelioma. The INITIATE trial was a single-arm phase 2 trial where researchers assessed nivolumab plus ipilimumab in patients with pleural mesothelioma after at least one line of platinum-containing chemotherapy.[44] Nivolumab 240 mg was given every 2 weeks and ipilimumab 1 mg/kg every 6 weeks up to 4 times. The primary endpoint was disease control rate. At 12 weeks, reported responses were 29% PR, 38% SD, and a DCR of 67%. The median PFS of 6.2 months, and OS at 12 months of 64%. Post-hoc analysis of treatment outcome according to PD-L1 expression status demonstrate that response in PD-L1 positive tumors (≥1%) were better (PR 47%, SD 40%, PD 13 %) when compared to PD-L1 negative samples (PR 16%, SD 37%, PD 47%). Safety data of the combination was consistent with known adverse events. 38% of the patients had grade 3 or 4 treatment-related adverse events. The same combination of ipilimumab and nivolumab was also studied in the IFCT-1501 MAPS2 trial, an open label, non-comparative, randomized phase 2 study for patients with pleural mesothelioma who had received one or two lines of prior therapy.[45] Patients were allocated to either nivolumab 3 mg/kg every 2 weeks alone or nivolumab with the addition of ipilimumab 1 mg/kg every 6 weeks. Of note, this trial was not powered for comparisons between the two groups. The primary outcome was 12 week DCR. 12-week DCR was observed in 40% of the nivolumab group vs 52% in the combination group. Of the 108 patients assessed, ORR was 19% in the nivolumab arm and 28% in the nivolumab plus ipilimumab arm. Both median PFS and OS were statistically significantly higher with the addition of ipilimumab. Median PFS was 4 months in the nivolumab arm (95% CI 2.8-5.7) vs 5.6 months in the nivolumab plus ipilimumab arm (95% CI 3.1-8.3). Median OS was 11.9 months in the nivolumab arm (95% CI 6.7–17.7) vs 15.9 months (10.7- not reached)

in the nivolumab plus ipilimumab arm. Of note, grade 3-4 treatment-related adverse events were higher in the combination group (26%) compared to the nivolumab group (14%). There were also three treatment related deaths in the combination arm (one fulminant hepatitis, one encephalitis, and one acute kidney failure).

Nivolumab plus Ipilimumab (CheckMate 743 Trial) as Front-Line Therapy: A New Standard of Care

CheckMate 743 was a randomized, open-label, phase 3 trial comparing the combination of nivolumab and ipilimumab to chemotherapy as first line therapy for patients with unresectable pleural mesothelioma.[46] Patients were given up to two years of treatment with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks or 6 cycles of pemetrexed and platinum therapy. Results from a prespecified interim analysis found a 4 month OS survival advantage with the immunotherapy combination compared to chemotherapy (18.1 vs 14.1 months; HR 0.74, 95% CI 0.60-0.91; P = 0.0020).[47] Median duration of response was 11.0 months in the immunotherapy combination group compared to 6.7 months in patients in the chemotherapy group. In a prespecified exploratory analysis based on histology, the subgroup of patients with epithelioid histology had a HR for OS of 0.85 (95% CI: 0.68, 1.06), with median OS of 18.7 months in the ipilimumab plus nivolumab arm and 16.2 months in the chemotherapy arm. In the subgroup of patients with non-epithelioid histology, the nivolumab and ipilimumab combination more than doubled OS compared to patients treated with chemotherapy, at 18.1 months vs. 8.8 months, respectively; HR 0.46, 95% CI 0.31-0.68. Response rates were comparable at 40% and 43% for the immunotherapy combination and chemotherapy regimen respectively. Serious adverse reactions occurred in 54% of patients treated with the immunotherapy combination immunotherapy, with the most frequent being pneumonia, fever, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism. Fatal adverse reactions occurred in four patients as a result of pneumonitis, acute heart failure, sepsis, and encephalitis. 23% of patients receiving immunotherapy permanently discontinued treatment due to adverse events and 52% had at least one discontinued due to adverse reactions.

Based on these trial results, the FDA subsequently approved nivolumab plus ipilimumab as first line treatment for adult patients with unresectable malignant pleural mesothelioma on October 2nd, 2020. Notably, the FDA approved dosing for the treatment is nivolumab 360 mg every 3 weeks and ipilimumab 1 mg/kg every 6 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.[48]

Given the survival benefit shown in this study, this combination of nivolumab and ipilimumab will be practice changing as first line therapy for patients with unresectable pleural mesothelioma. It is the first regimen over last 16 years that has led to FDA approval in mesothelioma and represent a meaningful advance for treatment of this deadly disease. Although the benefit of immunotherapy was greatest in patients with sarcomatoid histology we favor combination of ipilimumab with nivolumab as first-line therapy for patients with mesothelioma, irrespective of tumor histology. For patients with contraindications to receive immunotherapy, platinum and pemetrexed combination therapy is a viable treatment option.

Combination Studies of Immune Checkpoint Inhibitors

There has also been considerable interest in combining ICIs with different drugs to increase their efficacy such as chemotherapy, tyrosine kinase inhibitors, and oncolytic viruses. Currently, the agents that are in advanced stages of clinical trials are in combination with chemotherapy.

The DREAM trial was a single-arm Australian phase 2 trial to determine the safety of durvalumab combined with cisplatin and pemetrexed as first line therapy in pleural mesothelioma.[49] Fifty-four patients received durvalumab, 1125 mg, in combination with cisplatin and pemetrexed on day 1 of 3-week cycle for a maximum of 6 cycles, followed by durvalumab, 1125 mg, alone until progression or to 1 year total therapy. At 6 months, 57% were alive and progression free. At a median follow-up of 28 months, Objective tumor response was 48% with a median PFS of 6.9 months. Results from a phase 2 trial in the United States (PrE0505) using the same treatment regimen reported at the 2020 ASCO Annual meeting found a ORR of 56.4%, median PFS of 6.7 months, and median OS of 20.4 months in 55 patients.[50] Based on these promising results from Australia and the United States, the international, open label, phase 3 trial DREAM3R (NCT04334759) was initiated to compare the addition of durvalumab to standard platinum-based therapy vs standard platinum therapy in chemotherapy-naïve patients with mesothelioma.

The Beat-meso trial (NCT03762018) is a multi-institutional, randomized phase 3 study in Europe and the United Kingdom comparing the triplet therapy of bevacizumab, carboplatin, and pemetrexed to the quadruple therapy of bevacizumab, atezolizumab, carboplatin, and pemetrexed for newly diagnosed patients with pleural mesothelioma. The study enrollment goal is 320 patients with an estimated study completion date in 2024. IND.227 is a Canadian phase 2/3 trial currently comparing the combination of pembrolizumab, pemetrexed and cisplatin to pemetrexed and cisplatin in newly diagnosed patients with mesothelioma (NCT02784171).

The Mesothelioma Stratified Therapy (MiST) trial (NCT03654833) is another promising phase 2a trial for patients with relapsed mesothelioma that uses a multi-arm stratified trial design.[51] Prospective molecular profiling of *BAP1, BRCA1, p16ink4A*, and *PD-L1* expression using immunohistochemistry is performed on the tumors. Based on these results, patients are stratified into 4 different treatment groups: rucaparib for *BAP1* inactivated or *BRCA1* negative mesotheliomas; abemaciclib for *p16ink4a* negative tumors; pembrolizumab and bemcentinib for tumors without biomarker specifications; or atezolizumab and bevacizumab for PD-L1 positive mesothelioma. The primary endpoint will be 12 week DCR with response rates and 24 week DCR as secondary endpoints.

With the approval of nivolumab plus ipilimumab as initial therapy for patients with unresectable mesothelioma it will be of interest to see how other combination studies of immune checkpoints compare to these results. If positive, these trials would expand treatment options for these patients and improve their overall survival and quality of life.

MESOTHELIN-TARGETED THERAPIES

Mesothelin is a 40 kiloDalton (kDa) cell-surface glycoprotein that is expressed in low levels on normal mesothelial cells, but is highly expressed in many solid tumors, including mesothelioma, ovarian, pancreatic, and lung cancers.[52] Mesothelin overexpression has been implicated in promoting tumor invasion and malignant transformation.[53] Since its discovery in the early 1990s, a number of clinical trials have been conducted with mesothelin-targeted therapies, including antibody-drug conjugates, radioimmunoconjugates, T cell engagers, immunotoxins, and adoptive cellular therapies.[54] Of note, sarcomatoid mesotheliomas, which represent about 10-15% of cases, do not overexpress mesothelin and thus are not eligible for mesothelin-targeted therapy.

LMB-100 is an immunotoxin composed of a humanized anti-mesothelin Fab fused to a *Pseudomonas* exotoxin (PE). After LMB-100 binds to mesothelin-expressing cells, the PE enters the cell and triggers cell death by disrupting protein synthesis.[55] LMB-100 was investigated for safety and MTD in a phase 1 clinical trial enrolling patients with advanced pleural or peritoneal mesothelioma who have not responded to platinum therapy.[56] Following treatment with LMB-100, 9 patients received pembrolizumab and one patient received nivolumab as their next therapy. Durable responses were seen in four of these patients, with three partial responses and one complete response (CR). Notably, the patient with CR has continued to remain disease free post-treatment for over 37 months.[57] Based on these promising results, NCT03644550, a phase 2 trial at NCI, is currently recruiting patients with pleural and peritoneal patients who have progressed on platinum therapy for treatment with 2 cycles of LMB100 followed by pembrolizumab for up to 2 years.

Anetumab ravtansine is an antibody-drug conjugate composed of the human anti-mesothelin antibody, anetumab, linked to the maytansinoid tubulin inhibitor DM4. Based on promising phase 1 data, a phase 2 study enrolled 248 patients who had progressed on previous therapy to receive either anetumab ravtansine or vinorelbine.[58, 59] However, no statistically significant improvement in median PFS or OS between the two groups was noted. Median PFS was 4.3 months in the anetumab ravtansine group and 4.5 months in the vinorelbine group ($p = 0.859$). Median OS was 10.1 months with anetumab ravtansine and 11.6 months with vinorelbine ($p = 0.721$).

MSLN-TTC is a radioimmunoconjugate, consisting of the anetumab antibody, conjugated to a chelating agent, and labeled with the alpha-emitting radioisotope thorium-227. Preclinical data have reported that MSLN-TTC demonstrated tumor growth inhibition in cell and patient-derived xenograft tumor models.[60] An international phase 1 trial (NCT03507452) is recruiting patients with advanced recurrent epithelioid mesothelioma or serous ovarian cancer who have exhausted available therapeutic options.

HPN536 is a 50 kDa T cell engager that directs the patient's own T cells to kill the cells expressing mesothelin.[61] It is composed primarily of 3 components: 1) the anti-mesothelin single antibody domain that binds to mesothelin on tumor cells, 2) the single-chain variable fragment (scFv) that binds to the epsilon domain of CD3 antigen (CD3e) on T cells, and 3) the anti-albumin single domain antibody that binds to albumin to extend the drug

half-life. Patients with malignant mesothelioma with progressive disease after frontline platinum-based therapy are eligible to enroll in an open-label, phase 1/2a clinical trial (NCT03872206).

Adoptive Anti-mesothelin Cellular Therapy

There have also been several clinical trials using anti-mesothelin CAR T cells and with different routes of administration. CAR are genetically engineered receptors introduced into T cells that target specific cell surface antigens. The extracellular single chain antibody variable fragment (scFv) part of the CAR determines the antigen specificity of the CAR T cell. A group at the University of Pennsylvania (UPenn) generated a CAR T cell product using mRNA electroporation that transiently expressed the antimesothelin CAR on T cells to avoid potential on-target, off-tumor toxicity. They conducted a phase 1 trial by giving multiple intravenously administered CAR T cells to patients with pleural mesothelioma. No off tumor toxicities were reported but there were no reported clinical responses.[62] One patient developed an anaphylactic reaction after reinitiating CAR T cells infusions after a four week treatment interruption. This was attributed to anti-murine antibody responses to the murine scFv. Given the lack of off-tumor toxicities, the UPenn group subsequently transduced the same CAR with a lentivirus vector and treated five patients with mesothelioma with the engineered cells.[63] Best overall response was stable disease. The most recent UPenn phase 1 trial (NCT03054298) offers lentiviral-transduced CAR T cells with a fully human mesothelin-specific scFV for patients with advanced epithelioid mesothelioma who have failed previous therapies.

Memorial Sloan Kettering is also conducting a single center, open-phase 1/2 study (NCT02414269) of intrapleurally administered CAR T cells in patients with pretreated mesothelioma, lung cancer, or breast cancer.[64] These icasM28z CAR T cells use a 2nd generation CD28-costimulated fully human anti-mesothelin CAR with an inducible caspase-9 safety gene. A subset of patients treated with CAR T cells who received pembrolizumab off protocol showed anti-tumor responses. CAR T cells were detected in the blood of 13 of the 14 patients. Overall, intrapleural administration of MSLN-targeted CAR T cells was found to be safe and persistent.

T cell receptor fusion constructs (TRuCs) fuse the antigen-specific scFv to the N-terminus of the CD3e T-cell receptor (TCR) subunit, allowing them to be integrated directly into the endogenous T cell receptor complex.[65] This will presumably allow a more broad and controlled T cell response by utilizing all the TCR subunits. TC-210 is a intravenously administered mesothelin-specific TRuC that has been reported to have anti-tumor activity in animal models of lung, ovarian and mesothelioma cancers.[66] A phase 1 study (NCT03907852) is currently recruiting pretreated patients with pleural or peritoneal mesothelioma, serous ovarian adenocarcinoma, cholangiocarcinomas, or nonsquamous non-small cell lung cancer (NSCLC).

FUTURE OUTLOOK

Although multiple randomized phase 2 and 3 trials of novel anticancer agents for mesothelioma have been disappointing, the recent approval of nivolumab plus ipilimumab

for first line treatment of advanced mesothelioma, the first FDA approval since pemetrexed and cisplatin in 2004, is exciting news. It represents an important advance for treatment of this disease. However, even with this therapy, the median overall survival of patients with unresectable disease is only 18 months. Clearly, we need to develop better therapeutics to make a meaningful difference in the lives of these patients. Several studies are ongoing and if positive, will further improve treatment options for patients with mesothelioma. The results of immune checkpoint inhibitors with chemotherapy such as Beat-meso, IND.227, and the DREAM3R phase 3 trials are important studies whose results are eagerly awaited.

Mesothelin-targeted therapies have also rapidly progressed in recent years, with multiple trials conducted using antibody-drug conjugates, radioimmunoconjugates, T cell engagers, immunotoxins, and adoptive cellular therapies. Although many of these studies have been negative thus far, anti-mesothelin adoptive cellular therapy in mesothelioma has the potential to generate a targeted, persistent, and durable anti-tumor immune response alone or in combination with immune checkpoint inhibitors.

In summary, the future outlook for patients with mesothelioma is promising. There have been many advancements in the treatment of advanced mesothelioma which offers patients more treatment options beyond standard chemotherapy and opportunities to achieve better outcomes. Other therapies besides immune checkpoint inhibitors and mesothelin targeted agents are also encouraging and could lead to new options for this disease.

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Table 1:

Single agent immune checkpoint inhibitor trials in mesothelioma[a]

Checkpoint inhibitor (target)	First author	Clinical trials	Objective response rate (number of patients with response of total enrolled)	Comments	Clinical trial registry number and reference
Pembrolizumab (anti PD-1)	Alley et al., 2017	KEYNOTE-028, Ph 1b, 10 mg/kg every 2 wks up to 2 yrs	20% (5/25) PR	Median response duration 12m	NCT02054806 [35]
	Desai et al., 2018	Ph 2, 200 mg every 21 days	19% (12/65) PR	DC 66%, mPFS 4.5m, mOS 11.5m	NCT02399371 [36]
Nivolumab (anti PD-1)	Quispel-Janssen et al., 2018	Ph 2, 3mg/kg every 2 wks	24% (8/34) PR	12-wk DC 47%	NCT02497508 [38]
	Okada et al., 2019	MERIT, Ph 2, 240 mg every 2 wks	29% (10/34) ORR	Median duration of response 11.1m, 68% DC, mPFS 6.1m, mOS 17.3m	clinicaltrials.jp (JapicCTI-163247)[39]
Avelumab (anti PD-L1)	Hassan et al., 2019	JAVELIN, Ph 1b, 10 mg/kg every 2 wks	9% (5/53) ORR, 1 CR, 4 PR	Median duration of response 15.2m, DC 58%, mPFS 4.1m, mOS 10.7m	NCT01772004 [42]
Tremelimumab (anti CTLA-4)	Calabro et al., 2013	Ph 2, 15 mg/kg every 90 day	7% (2/29) PR	DC 31%, mPFS 6.2m, mOS 10.7m	NCT01649024 [32]
	Calabro et al., 2015	Ph 2, 10 mg/kg every 4 wks for 6 doses then every 12 wks	3% (1/29) PR	4/29 immune related PR, DC 52%, median duration 10.9m	NCT01655888 [33]
	Maio et al., 2017	Ph 2b, DETERMINE, same dose and schedule as above, treated (382) vs placebo (189)		mOS not different between tremelimumab (7.7m) vs placebo (7.3m)	NCT01843374 [34]

[a]Studies that have been published or presented as abstracts are included.

Abbreviations: CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, disease control; m, months; mOS, median overall survival, mPFS, median progression free survival; ORR, objective response rate; PD-1, Programmed cell death-1; PD-L1, Programmed cell death ligand-1; Ph, Phase; PR, partial response; wks, weeks; yrs, years

Table 2:

Combination therapies with multiple immune checkpoint inhibitors or immune checkpoint inhibitor with chemotherapy or other agents in mesothelioma[a].

Drugs	First author	Clinical trials	Objective response rate	Comments	Clinical trial registry number and reference
Tremelimumab + Durvalumab	Calabro et al., 2018	Ph 2, NIBIT-MESO-1 Combination therapy every 4 wks for 4 doses, followed by maintenance durvalumab for 9 doses	28% (11/40) immune related OR	Median immune related PFS 8m, mPFS 5.7m, mOS 16.6m	NCT0258813 [43]
Nivolumab + Ipilimumab	Disselhorst et al., 2019	Ph 2, INITIATE, Nivolumab 240 mg every 2 wks plus ipilimumab 1 mg/kg every 6 wks up to 4 times	29% (10/34) PR	DC 68%, marked efficacy	NCT03048474 [44]
	Scherpereel et al., 2019	Ph 2, IFCT-1501 MAPS2, Nivolumab (3mg/kg every 2 wks) vs Nivolumab + Ipilimumab (1mg/kg every 6 wks)	40%	12-wk DC: 44% (24/54) in nivolumab vs 50% (27/54) in combination group	NCT02716272 [45]
	Baas et al., 2020	Ph 3, CheckMate743, Nivolumab (360mg every 3 wks) + Ipilimumab (1 mg/kg every 6 wks) vs chemotherapy as 1st line therapy	40%	mOS 18.1m in nivo + ipi vs 14.1m in chemotherapy arm. Median duration of response 11m vs 6.7m	NCT02899299 [47, 48]
Durvalumab + cisplatin + pemetrexed	Nowak et al., 2020	DREAM, Ph 2	48%	6m-PFS 57%, mPFS 6.9m	ANZ Clinical trial registry number: ACTRN12616001170415[49]
	Forde et al, 2020	PrE0505, Ph 2		mOS 21.1m	NCT02899195 [50]
Pembrolizumab vs Gemcitabine or Vinorelbine	Popat et al., 2020	PROMISE MESO, Ph 3	22% in pembrolizumab vs 6% in chemotherapy arm	mPFS 2.5m in pembrolizumab vs 3.4m in chemotherapy, mOS 10.7m vs 11.7m	NCT02991482 [37]

[a]Studies that have been published or presented as abstracts are included.

Abbreviations: DC, disease control; m, months; mOS, median overall survival, mPFS, median progression free survival; OR, objective response; Ph, Phase; PR, partial response; wks, weeks; yrs, years

Table 3:

Selected recently completed or ongoing randomized phase 2/3 studies of immune checkpoint inhibitors alone, or in combination with chemotherapy or other agents in mesothelioma treatment

Drugs	Clinical trials	Comments[¶]	NCT
Immune checkpoint inhibitors + chemotherapy			
Pembrolizumab vs pembrolizumab + cisplatin + pemetrexed	Ph 2, 3, recruiting	First line therapy	NCT02784171
Durvalumab + cisplatin + pemetrexed vs cisplatin + pemetrexed	DREAM3R, Ph 3, not yet recruiting	First line therapy	NCT04334759
Bevacizumab + carboplatin + pemetrexed vs bevacizumab + atezolizumab + carboplatin + pemetrexed	BEAT-meso, Ph 3, recruiting	First line therapy	NCT03762018
Immune checkpoint inhibitors, single agent			
Pembrolizumab	Ph 2, complete		NCT02399371
Nivolumab	CONFIRM, Ph 3, nivolumab vs placebo, ongoing		NCT03063450 [41]
Durvalumab	Ph 2, Active, not recruiting		NCT04115111
	Ph 2, Active, not recruiting		NCT02899195
Immune checkpoint inhibitors in combination with other therapies			
Pembrolizumab + iCasp9M28z T cell infusions + cyclophosphamide	Ph 1/2, recruiting	MSLN targeting CAR T cells	NCT02414269
Pembrolizumab + INCB001158	Ph 1/2, recruiting	Arginase inhibitor	NCT02903914
Pembrolizumab + bemcentinib	MiST, Ph 2, recruiting	AXL kinase inhibitor	NCT03654833
Pembrolizumab + defactinib	FAK-PD1, Ph 1/2, recruiting	Focal adhesion kinase inhibitor	NCT02758587
Pembrolizumab + LMB-100	Ph 2, recruiting	MSLN targeting immunotoxin	NCT03644550
Pembrolizumab w/wo anetumab ravtansine	Ph 1/2, recruiting	MSLN directed ADC	NCT03126630
Nivolumab + ipilimumab	Ph 2, recruiting		NCT02834013
	Ph 1/2, recruiting		NCT03918252
Nivolumab + ipilimumab + INCAGN01949	Ph 1/2, complete	Anti OX40	NCT03241173
Nivolumab + ipilimumab + INCAGN01876	Ph 1/2, recruiting	Anti-human glucocorticoid-induced tumor necrosis factor receptor	NCT03126110
Nivolumab + ipilimumab + UV1 vaccine	Ph 2, recruiting	Cancer vaccine	NCT04300244
Nivolumab + MTG 201	Ph 2, recruiting	Reduced Expression in Immortalized Cells/ Dickkopf-3 gene (REIC/ Dkk-3 gene)	NCT04013334
Nivolumab + ramucirumab	Ph 2, recruiting	Anti-VEGFR2	NCT03502746

Abbreviations: ADC, antibody-drug conjugate; CAR T, chimeric antigen receptor T cells; MSLN, mesothelin; OX40, Tumor necrosis factor receptor superfamily, member 4; Ph, Phase; VEGFR2, Vascular endothelial growth factor receptor 2

[¶]Combination drug information