Immunotherapy in malignant peritoneal mesothelioma (Review)

SABAH ALAKLABI[1], ARYA MARIAM ROY[1], JOSEPH J. SKITZKI[2] and RENUKA IYER[1]

Departments of [1]Medicine and [2]Surgical Oncology/Immunology,
Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, USA

Received October 19, 2022; Accepted January 5, 2023

DOI: 10.3892/mco.2023.2627

Abstract. Over the last decade, there has been a movement in cancer treatment away from cytotoxic therapies toward strategies that enhance the immune system against cancer. Immune checkpoint inhibitors (ICIs) have been incorporated into the treatment regimens for patients with various solid tumors. Mesothelioma trials revealed encouraging efficacy; however, patients with peritoneal mesothelioma are usually excluded, slowing the progress of improving the treatment of this aggressive cancer and compelling oncologist to rely on retrospective studies despite their flaws and limitations. Currently, there is no consensus on the role of ICIs in the treatment of malignant peritoneal mesothelioma (MPeM). The present review discusses data from clinical studies that examined immunotherapy in MPeM and evaluates what is known about the relevance of the tumor microenvironment and clinically validated biomarkers for ICIs efficacy. Furthermore, a proposed strategy for utilizing immunotherapy in treating MPeM is discussed.

Contents

1. Introduction

Malignant peritoneal mesothelioma (MPeM) arises from the mesothelial cells lining the peritoneum and has been linked to asbestos exposure (1-4). MPeM is an extremely uncommon form of cancer, accounting for only about one-fifth of all mesotheliomas. It was projected that there will be 15,000 new cases of MPeM diagnosed in the United States between the years 2005 and 2050 (5-7). According to a large study using the Surveillance, Epidemiology, and End Results (SEER) database, overall patients who had MPeM had a five-year survival rate of 20.3%. The impact of different treatment modalities on the 5-year overall survival (OS) rates was reported to be 43.5% for patients who underwent surgery alone, 25.9, and 18.7% for those who had radiation only, or chemotherapy alone, respectively (8). The majority of patients are symptomatic at presentation. The most common complaints are abdominal distention or pain, loss of weight, dyspnea, and chest pain (9,10). In the frontline for disease management, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) continue to be the mainstay of treatment based on well-designed retrospective case-control and cohort studies (11,12). Immune checkpoint inhibitors (ICIs), either alone or in conjunction with chemotherapy, have gained a lot of attention as a potential treatment option for patients with mesothelioma in recent years. The majority of these studies have focused on pleural mesothelioma patients, and it is unclear whether or not these results are applicable to MPeM patients. In this article, we focus on reviewing recently published studies of immunotherapy in the treatment of inoperable MPeM.

2. MPeM tumor microenvironment and clinically established biomarkers for immune checkpoint inhibitors (ICIs) efficacy

Over the last decade, there has been a movement in cancer treatment away from cytotoxic therapies toward strategies that enhance the immune system against cancer. ICIs targeting programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PDL1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) have been incorporated into the treatment regimens for patients with various solid tumors. In mesothelioma, most of the trials are conducted in pleural mesothelioma excluding MPeM patients. The validation of multiple predictive biomarkers of ICIs' efficacy have been accomplished across a variety of tumor types, including PDL1, tumor mutational burden (TMB), and microsatellite instability (MSI) as examples.

Programmed cell death ligand 1 (PDL1). According to a small study that examined 13 peritoneal samples, PDL1 was

Correspondence to: Dr Renuka Iyer, Department of Medicine, Roswell Park Comprehensive Cancer Center, 665 Elm & Carlton Streets, Buffalo, NY 14263, USA
E-mail: renuka.iyer@roswellpark.org

Key words: peritoneal mesothelioma, immune checkpoint inhibitors, efficacy, tumor microenvironment, clinical trials

expressed in a significant portion of malignant mesothelioma. They found the percentage of tissue microarray samples positive for PDL1 expression (defined as >1% tumor staining) using two FDA-approved immunohistochemistry markers to be significantly higher in MPeM (50-60%), than in pleural mesothelioma (18-22%). Another more recent study supported the finding of high frequency of PDL1 expression in patients with MPeM (13). These results in addition to the available evidence of the complex pro-inflammatory microenvironment present in MPeM provided the foundation and reasoning for investigating immune-based treatment strategies like PDL1 inhibition with ICIs. The findings also supported investigating PDL1 as a potential biomarker for immunotherapy benefit in a subset of MPeM patients in clinical trials (14-16). Interestingly, PDL1 expression is temporally heterogeneous in MPeM. This has been linked to past exposure to cytotoxic chemotherapy as it was shown that patients who received systemic chemotherapy in the past had a significantly lower frequency of PDL1 expression (6% vs. 16%) (17). This highlights the importance of determining the optimal treatment sequence for successful outcomes and should be taken into account when planning future clinical studies. For the time being, there is no consensus on selecting patients with MPeM who would benefit from therapies that target PD-1 using the expression of PDL1.

Microsatellite instability (MSI). It has been demonstrated that tumors with high levels of microsatellite instability (MSI-H) are hypermutated and produce many peptides that function as neoantigens, causing a robust immune response that is characterized by a high number of tumor-infiltrating lymphocytes (TILs) (18-21). Previous evidence has shown that MSI-H cancers are responsive to treatment with PD-1 ICIs (22). One example is colorectal cancer, which demonstrated an impressive and durable response to ICIs (18,23-25). Colorectal, endometrial, and gastric adenocarcinomas are the most common cancers in which MSI has been identified (26,27). Unfortunately, the occurrence of MSI-H in mesothelial cancer is extremely rare (28). In the rare event of identifying MSI-H, pembrolizumab, which is a PD-1 inhibitor, was granted approval by the FDA in May 2017 for the treatment of advanced solid tumors, including mesothelioma, that has MSI-H and have progressed following prior treatment, and for which there are no alternative treatment options that are considered to be satisfactory.

Tumor mutational burden (TMB). Immunotherapy appears to be more effective in cancers with high tumor mutation burden (TMB-H) (defined as 10 or more mutations per megabase), such as melanoma and non-small cell lung carcinoma (29,30). Mesothelioma patients have the lowest prevalence of TMB-H across all solid malignancies (1.2%) (31). Of note, patients with MPeM who have a higher somatic mutational burden, had a significant increase in PDL1 staining. The same finding of a significant increase in PDL1 staining was noted in patients with known deleterious germline mutations (17). Again, pembrolizumab was granted accelerated approval by the FDA in June of 2020 for the treatment of unresectable or metastatic solid tumors with TMB-H in patients who have progressed in response to prior treatment and have no alternative treatment options that are considered to be satisfactory.

Tumor-infiltrating lymphocytes (TILs). The immunological microenvironment of MPeM is little understood. Pleural mesothelioma has taught us that TILs may have an impact on the prognosis of patients with mesothelioma. TILs were reported to have a favorable prognostic effect in pleural mesothelioma in early immunohistochemistry (IHC)-based research (32,33). Conversely, a strong negative correlation was found between the stromal TILs score and survival in a cohort of 329 pleural malignant mesothelioma. Nevertheless, the presence of tertiary lymphoid structures (TLS), which serve as access points for TILs entry and local priming, was independently associated with higher survival when multivariate analysis was performed (34). The evaluation of immune infiltrates in tumors, is gaining importance as a prognostic and potentially predictive biomarker to select patients who have the highest likelihood of responding to immunotherapeutic agents. TILs assessment has not been established as a clinical biomarker yet; however, it has been suggested to include it in the routine histopathological reporting (35-37). TILs have been thought of as a favorable prognostic marker however, some patients with high TILs levels may not have a better prognosis. A possible explanation is that TILs levels measured on hematoxylin and eosin (H&E) may not reflect levels of active anti-tumor TILs reflecting functional inhibition. TILs may be exhausted or rendered inactive by immune checkpoint pathways signaling or by a lack of immune stimulatory pathways which both can be reactivated through immunotherapy (38,39). Alternatively, generic TILs detection by H&E may not account for T regs or other immunosuppressive populations (40-42).

Epithelial-to-mesenchymal transition (EMT) gene score. EMT genes are unique potential targets that can be used to halt the progression of cancer and its spread (43). It has been demonstrated that EMT plays an essential role in the process of carcinogenesis, as well as the progression of cancer, invasion, and metastasis (44). Cancer cells can reactivate EMT pathways within their genomes and become more aggressive. EMT is linked to increased cancer stemness, which in turn drives cancer spread, recurrence, and resistance to treatment (43,45,46). It has been proposed in preclinical research that tumor cell EMT levels influence immunosuppression, with tumors with higher EMT levels being resistant to immunotherapy (47,48). The prognosis and therapeutic response can both be possibly predicted by characterizing EMT. Prior studies have shown that transcriptional factors involved in EMT cause immunosuppressive cells to infiltrate the tumor, creating an immunosuppressive microenvironment. Consequently, EMT in tumor cells is promoted by the immunosuppressive cells. Cancer progression is promoted by the interaction between EMT and immunosuppression indicating that EMT may develop as an important biomarker in the perspective of immunotherapy (49-51).

In a recent study on pleural mesothelioma, a panel of four EMT genes (COL5A2, ITGA, SPARC, and ACTA2) were identified and their overexpression in epithelioid mesothelioma was associated with poor prognosis, demonstrating that these genes have the potential to function as independent prognostic markers in this subtype of mesothelioma. In addition, overexpression of these genes was associated with the immunosuppressive microenvironment driven by EMT. Therefore,

it was suggested that these genes may serve as predictive biomarkers for immunotherapy selection (52).

EMT was studied in MPeM, during a phase 2 single-center basket trial for the assessment of atezolizumab/bevacizumab in MPeM. The investigators concluded that transcriptome mesenchymal differentiation is a predictor of poor outcomes in MPeM when treated with atezolizumab/bevacizumab combination including those with epithelioid histology. Higher EMT gene scores were associated with poorer progression-free survival (PFS) on both atezolizumab/ bevacizumab and prior platinum pemetrexed chemotherapy. This finding is in line with prior evidence of EMT gene-signature score prognostic value in pleural mesothelioma (53,54). Moreover, they correlated baseline EMT gene expression scores with therapeutic resistance and response. A low EMT gene score was found to be a predictor of response even among patients with epithelioid subtype.

BRCA1 associated protein 1 (BAP1). Both pleural and peritoneal mesotheliomas have been associated with sporadic and germline BAP1 mutations. MPeM with BAP1 mutation have 7-fold improved long-term survival (55,56). In a comprehensive genomic, transcriptomic, and proteomic investigation of 19 patients with MPeM, BAP1 deletions were linked to a more inflammatory tumor microenvironment. PDL1 and other immune checkpoint molecules were found to be highly expressed in BAP1-altered MPeM. The suggestion that BAP1 deletions may be utilized as a marker of ICIs responsiveness stems from these findings (57).

3. Immune checkpoint inhibitors in peritoneal mesothelioma

Beyond pemetrexed combination regimens used in the first-line setting, there is no accepted standard of care in MPeM (58-63). The addition of bevacizumab to pemetrexed plus cisplatin was found to increase OS in malignant pleural mesothelioma, therefore it has been into consideration to use in MPeM (64). Because of the exclusion of MPeM from mesothelioma clinical trials, there is a lack of prospective evidence of ICIs efficacy with the majority of evidence extrapolated from pleural mesothelioma and anecdotes and retrospective studies.

ICIs have been administered off-label for the treatment of peritoneal mesothelioma due to encouraging outcomes seen in malignant pleural mesothelioma. This practice is unsupported since the benefit of first-line immunotherapy in pleural mesothelioma was greatest in patients with nonepithelial tumors, whereas the majority of MPeM are epithelial, and due to the immunological and molecular differences between the two cancers making extrapolating pleural data to peritoneal disease questionable (16).

Monotherapy. Multiple ICIs were studied as a single agent for the treatment of mesothelioma in general, including MPeM. The efficacy and toxicity of avelumab, an anti-PDL-1 was evaluated in phase 1b open-label study (JAVELIN Solid Tumor) in patients with mostly pleural and peritoneal mesothelioma that progressed after platinum and pemetrexed treatment. It was a single-arm study with 53 patients enrolled. Of note, the exact number MPeM patients was not reported. The study reported a low overall response rate (ORR) of about 10% all of which were partial responses (PR). Although modest in terms of response rate, responses were durable with a median duration of response of 15 months. Notably, the ORR was significantly higher in the subset of patients that had what they defined as high PDL1 expression (>5%). The disease control rate (DCR) was 58%. Median PFS was 4.1 months, and the median OS was 10.7 months. Safety data were reassuring, with no treatment-related deaths, and a 9% rate of grade 3 or 4 treatment-related adverse events. No inference can be made regarding the efficacy of avelumab in the MPeM since treatment outcomes were not analyzed by disease location (65).

CONFIRM was a placebo-controlled, double-blind, randomized trial to evaluate the efficacy and safety of nivolumab, an anti-PD-1 antibody in pretreated pleural or peritoneal mesothelioma, who had prior platinum-based chemotherapy in the first line. They enrolled 332 patients out of which 16 (5%) patients had MPeM. They were randomly assigned (2:1) to receive nivolumab at a flat dose of 240 mg every 2 weeks or placebo until disease progression or a maximum of 12 months. Patients were stratified by epithelioid vs. non-epithelioid histology. 88% of both arms had epithelioid histology, and 34% of patients had a tumor proportion score (TPS) of at least 1% indicating expression of PDL1. Nivolumab was a 3rd line treatment for more than half the patients. With a median follow-up of 11.6 months, nivolumab showed superior PFS with a median of 3 months vs. 1.8 months in the placebo arm. Median OS was also superior with 10.2 months in the nivolumab group vs. 6.9 months in the placebo group. In the nivolumab group, 41% of patients had serious adverse events (AEs), whereas 44% of placebo group patients did. There were no treatment-related deaths in either group. It's not clear from this trial if nivolumab performs better than single agent conventional chemotherapy in the 2nd line setting of treatment of MPeM given that it was compared to placebo. The majority of patients had pleural mesothelioma and a different trial that was conducted in pleural mesothelioma compared pembrolizumab to single agent chemotherapy and did not detect any difference in survival (66,67).

DETERMINE, was a negative phase 2b double-blind, placebo-controlled study that involved 105 centers across 19 countries of tremelimumab (antibody against CTLA-4) in patients with advanced malignant mesothelioma who had received prior one or two systemic treatments for advanced disease. Single-agent tremelimumab showed no survival benefit over placebo. Due to the fact that there were only 26 (5%) patients with MPeM included (out of a total of 571 patients with mesothelioma), subgroup analysis for efficacy specifically in MPeM was not feasible. It's possible that the use of a single anti-CTLA-4 agent in addition to the selection of a particular anti-CTLA-4 agent contributed to the lack of efficacy that was seen in the study (68).

Pembrolizumab was evaluated in a phase II study with 64 patients who had previously been treated for mesothelioma with no more than two prior lines of chemotherapy, including pemetrexed and platinum. Of those 64 patients, 8 patients (12.5%) had MPeM. Epithelioid was the predominant histology (76.6%), followed by biphasic (15.6%) and sarcomatoid (7.8%). In this study, the patients who had pleural mesothelioma demonstrated higher ORR than those who with MPeM (pleural

20%, peritoneal 12.5%). The response rate was analyzed by histology, with the highest response seen in sarcomatoid histology (40%). The response rate was reported to be 16% in epithelioid, and 10% in biphasic. It was noted that PDL1 expression was more common in the peritoneal subset with 25% of MPeM patients classified as having PDL1 high tumor (defined as TPS greater than or equal to 50%), 50% had PDL1 low (TPS 1 to 49%), and 25% of MPeM patients were PDL1 negative (TPS less than 1%). No threshold for PDL1 efficacy was determined from this study and there was no correlation found between the expression of PDL1 and response rate as a continuous metric. However, there was a trend to higher response rate and more durable PFS with increasing PDL1 expression (69).

A retrospective case series of 13 patients with MPeM who received pembrolizumab reported the treatment outcomes. All patients had received prior chemotherapy. The majority of the patient's histology was epithelioid (70%) followed by biphasic (15%), sarcomatoid, and desmoplastic (7.7% for each). Independent of the level of PDL1 expression or histology, pembrolizumab demonstrated an ORR of 18% all of which are PR. DCR was reported to be 81%, with a median PFS of 5.7 months. Median OS was reported to be 20.9 months. Of note, three patients had a PFS of more than 2 years (70).

In summary, due to the small number of MPeM patients treated in clinical trials, no definitive conclusion can be drawn about the efficacy of single agent immunotherapy in previously treated peritoneal mesothelioma. Response rates seem to be low and occur mainly in non-epithelioid histology. Additionally, it is unknown if PDL1 expression is predictive of benefit. Nevertheless, pembrolizumab remains a reasonable option on the rare occasion of high TMB and MSI-H MPeM.

Immune checkpoint inhibitors combination. Despite the drawbacks of extrapolating from pleural disease, combination immunotherapy has been used in MPeM due to its FDA approval and established efficacy in pleural mesothelioma. In malignant pleural mesothelioma, combination ICI-based treatment has shown encouraging success rates. In checkmate 743 which did not include any patients with MPeM, combination PD-1 and CTLA-4 inhibition with nivolumab and ipilimumab in treatment naïve malignant pleural mesothelioma significantly increased OS (median 18.1 months) compared to chemotherapy (median 14.1 months) (71).

The combination of tremelimumab plus durvalumab (anti-PDL1 monoclonal antibody) appears to result in clinically meaningful outcomes in mesothelioma. The single-arm phase II NIBIT-MESO-1 study that enrolled both treatment naïve and pretreated patients demonstrated an ORR of 28%, a DCR of 65%, and a median OS of 16.5 months. Despite the limited number of MPeM patients (2/40 (5%) enrolled), these results could support the use of tremelimumab combined with durvalumab in patients with MPeM given the OS benefit observed. The 4 years follow-up study suggested that retreatment may be safe and could still result in clinically meaningful outcomes (72,73).

A retrospective study conducted at a single institution in 29 patients with MPeM, reported an ORR of 19.2% following treatment with either a single agent ICI in 9 patients or a combination of nivolumab and ipilimumab in the remaining 20 patients. With a median follow-up of 9.8 months, 24 patients had discontinued ICIs (20 experienced progressive disease, 3 died, and 1 experienced toxic effects). The DCR was 65.4%. They reported a median PFS of 5.5 months and median OS of 19.1 months (74).

To recapitulate, no firm recommendation can be made about the use of combination ICIs in patients with MPeM at this time, given the absence of conclusive evidence that proves its safety and efficacy.

Combination chemoimmunotherapy. Chemoimmunotherapy showed favorable outcomes in pleural mesothelioma in the frontline setting. Patients with previously untreated, unresectable pleural mesothelioma were enrolled in PrE0505, a phase 2, single-arm, multicenter study. Patients received durvalumab (at a fixed dose of 1,120 mg intravenously) given once every 3 weeks in combination with pemetrexed and platinum at their standard doses for up to six cycles. Patients with stable or responding tumors after concurrent therapy continued on maintenance durvalumab for a maximum duration of 1 year. The primary endpoint of the study was OS which was met with combination of durvalumab/platinum/ pemetrexed also with a median OS of 21.1 months (75).

In MPeM, data are absent. In an intriguing case report, two patients with metastatic MPeM unresponsive to pemetrexed and platinum therapy, were treated with pembrolizumab in addition to pemetrexed /platinum, had a near-complete response in one patient and a remarkable partial response lasting 14 months in the other. Interestingly, both patients' tumors were PDL-1 negative and had low TMB. This provokes questions about the efficacy of chemoimmunotherapy in MPeM (76).

Vascular Endothelial Growth Factor (VEGF)/Vascular Endothelial Growth Factor Receptor (VEGFR) Pathway and Immune Checkpoint Inhibitor Combinations.

VEGF/VEGFR pathway inhibition in combination with chemotherapy resulted in minimal to no benefit at all in malignant pleural mesothelioma (64,77).

A cohort of 20 patients with MPeM was studied in an open-label, single-center basket trial for the assessment of atezolizumab/bevacizumab in a range of advanced uncommon malignancies. The study's objective was to evaluate the efficacy and safety of atezolizumab/bevacizumab in advanced MPeM who had previously failed systemic treatment with platinum-pemetrexed chemotherapy. There were only two patients with biphasic histology (10%), and all remaining patients had epithelioid histology. 12 patients (60%) had prior CRS and HIPEC in addition to systemic chemotherapy that all patients have received prior (53). An ORR of 40% was reported, with a median duration of response of 12.8 months. The 1-year OS rate of 86% seems meaningful when compared to the 1-year OS rate of (45-56%) reported in patients with prior platinum pemetrexed therapy (59,60,78). When compared to the previously reported 1-year OS rate of (45-56%) in patients with prior platinum pemetrexed treatment, the observed 1-year OS rate of 86% is considered significant.

Again, no correlation was found between atezolizumab/bevacizumab efficacy and PDL1 or TMB, and all tumors were microsatellite stable (MSS) which is consistent with the extreme rarity of MSI in mesothelioma (28). Since there was a role for EMT gene signature in predicting the prognosis of malignant pleural mesothelioma and diminishing

ICIs responses in lung cancer, the EMT gene-signature scores were tested in this study. They demonstrated that transcriptome mesenchymal differentiation could predict poor outcomes with atezolizumab/bevacizumab therapy in MPeM, with higher EMT gene scores in mesenchymal phenotype being associated with resistance to atezolizumab/bevacizumab (54,79). Grade 3 AEs were reported in 50% of patients with the most common being hypertension (40%) and anemia (10%). Grade 3 immune-related AEs were reported in 10% of patients and required treatment discontinuation.

More definite evidence of efficacy and safety given the fact that there is a higher risk of intestinal perforation with bevacizumab in peritoneal mesothelioma patients is needed.

4. Future directions

The previous sections have discussed the currently available clinical trials data employing ICIs in MPeM. It is worth acknowledging the efforts investigating the role of cellular immunotherapy in mesothelioma and we eagerly await the results of these trials (80,81).

In conclusion, given the lack of clear evidence to suggest that ICIs are superior to chemotherapy in the first line treatment of MPeM, it may be reasonable to reserve them for use in later lines given possible tolerance over chemotherapy, despite the lack of evidence to support this approach.

Finally, we recognize that the slow progress in the treatment of MPeM is due in part to the lack of incentive for drug developers to study rare malignancies due to the limited prospective market and the public sector inclination to focus on funding those with the highest need. In addition, randomized controlled trials, recognized as the gold standard for determining a treatment's or intervention's efficacy, are difficult to execute because of the challenges associated with patient accrual. While logistical barriers and cultural differences make it difficult to conduct trials on a global scale, doing so may assist in expanding the pool of eligible patients and addressing accrual issues.

For the time being, higher-level evidence for utilizing immunotherapy in the treatment of peritoneal mesothelioma may be provided by multicenter retrospective studies that incorporate uncontrolled trials and/or observational studies to address the current evidence gaps.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

The paper was conceptualized by SA, and the validation of the topic's relevance and significance was performed by RI and AMR. SA and AMR wrote the original draft. RI and JJS reviewed and edited the final paper. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Husain AN, Colby T, Ordonez N, Krausz T, Attanoos R, Beasley MB, Borczuk AC, Butnor K, Cagle PT, Chirieac LR, *et al*: Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 137: 647-667, 2013.
2. Bridda A, Padoan I, Mencarelli R and Frego M: Peritoneal mesothelioma: A review. MedGenMed 9: 32, 2007.
3. Teta MJ, Mink PJ, Lau E, Sceurman BK and Foster ED: US mesothelioma patterns 1973-2002: Indicators of change and insights into background rates. Eur J Cancer Prev 17: 525-534, 2008.
4. Selikoff IJ, Hammond EC and Seidman H: Latency of asbestos disease among insulation workers in the United States and Canada. Cancer 46: 2736-2740, 1980.
5. Moolgavkar SH, Meza R and Turim J: Pleural and peritoneal mesotheliomas in SEER: Age effects and temporal trends, 1973-2005. Cancer Causes Control 20: 935-944, 2009.
6. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, Chirieac LR, Dacic S, Duhig E, Flieder DB, *et al*: The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 10: 1243-1260, 2015.
7. Beebe-Dimmer JL, Fryzek JP, Yee CL, Dalvi TB, Garabrant DH, Schwartz AG and Gadgeel S: Mesothelioma in the United States: A surveillance, epidemiology, and end results (SEER)-Medicare investigation of treatment patterns and overall survival. Clin Epidemiol 8: 743-750, 2016.
8. Ullah A, Waheed A, Khan J, Mishra A, Tareen B, Nama N, Karki NR, Panezai MS, Zarate LV, White J, *et al*: Incidence, survival analysis and future perspective of primary peritoneal mesothelioma (PPM): A population-based study from SEER Database. Cancers (Basel) 14: 942, 2022.
9. Kaya H, Sezgı C, Tanrıkulu AC, Taylan M, Abakay O, Sen HS, Abakay A, Kucukoner M and Kapan M: Prognostic factors influencing survival in 35 patients with malignant peritoneal mesothelioma. Neoplasma 61: 433-438, 2014.
10. Antman KH: Clinical presentation and natural history of benign and malignant mesothelioma. Semin Oncol 8: 313-320, 1981.
11. Sugarbaker PH: Update on the management of malignant peritoneal mesothelioma. Transl Lung Cancer Res 7: 599-608, 2018.
12. Turaga KK, Deraco M and Alexander HR: Current management strategies for peritoneal mesothelioma. Int J Hyperthermia 33: 579-581, 2017.
13. Gazivoda VP, Kangas-Dick AW, Greenbaum AA, Roshal J, Chen C, Moore DF, Langan RC, Kennedy TJ, Minerowicz C and Alexander HR: Expression of PD-L1 in patients with malignant peritoneal mesothelioma: A pilot study. J Surg Res 277: 131-137, 2022.
14. Judge S, Thomas P, Govindarajan V, Sharma P and Loggie B: Malignant Peritoneal Mesothelioma: Characterization of the inflammatory response in the tumor microenvironment. Ann Surg Oncol 23: 1496-1500, 2016.

15. Tazzari M, Brich S, Tuccitto A, Bozzi F, Beretta V, Spagnuolo RD, Negri T, Stacchiotti S, Deraco M, Baratti D, *et al*: Complex Immune Contextures Characterise Malignant Peritoneal Mesothelioma: Loss of adaptive immunological signature in the more aggressive histological types. J Immunol Res 2018: 5804230, 2018.
16. Chapel DB, Stewart R, Furtado LV, Husain AN, Krausz T and Deftereos G: Tumor PD-L1 expression in malignant pleural and peritoneal mesothelioma by Dako PD-L1 22C3 pharmDx and Dako PD-L1 28-8 pharmDx assays. Hum Pathol 87: 11-17, 2019.
17. White MG, Schulte JJ, Xue L, Berger Y, Schuitevoerder D, Vining CC, Kindler HL, Husain A, Turaga KK and Eng OS: Heterogeneity in PD-L1 expression in malignant peritoneal mesothelioma with systemic or intraperitoneal chemotherapy. Br J Cancer 124: 564-566, 2021.
18. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, *et al*: PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372: 2509-2520, 2015.
19. Palmieri G, Colombino M, Cossu A, Marchetti A, Botti G and Ascierto PA: Genetic instability and increased mutational load: Which diagnostic tool best direct patients with cancer to immunotherapy? J Transl Med 15: 17, 2017.
20. Jamieson NB and Maker AV: Gene-expression profiling to predict responsiveness to immunotherapy. Cancer Gene Ther 24: 134-140, 2017.
21. Chalmers ZR, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, Schrock A, Campbell B, Shlien A, Chmielecki J, *et al*: Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 9: 34, 2017.
22. Chang L, Chang M, Chang HM and Chang F: Microsatellite instability: A predictive biomarker for cancer immunotherapy. Appl Immunohistochem Mol Morphol 26: e15-e21, 2018.
23. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, *et al*: Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357: 409-413, 2017.
24. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz H-J, Morse MA, Desai J, Hill A, Axelson M, Moss RA, *et al*: Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): An open-label, multicentre, phase 2 study. Lancet Oncol 18: 1182-1191, 2017.
25. Overman MJ, Lonardi S, Wong KYM, Lenz HJ, Gelsomino F, Aglietta M, Morse MA, Van Cutsem E, McDermott R, Hill A, *et al*: Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol 36: 773-779, 2018.
26. Imai K and Yamamoto H: Carcinogenesis and microsatellite instability: The interrelationship between genetics and epigenetics. Carcinogenesis 29: 673-680, 2008.
27. Watson P and Lynch HT: The tumor spectrum in HNPCC. Anticancer Res 14 (4B): 1635-1639, 1994.
28. Bonneville R, Krook MA, Kautto EA, Miya J, Wing MR, Chen HZ, Reeser JW, Yu L and Roychowdhury S: Landscape of microsatellite instability across 39 cancer types. JCO Precis Oncol 2017: PO.17.00073, 2017.
29. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, *et al*: Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 348: 124-128, 2015.
30. Johnson DB, Frampton GM, Rioth MJ, Yusko E, Xu Y, Guo X, Ennis RC, Fabrizio D, Chalmers ZR, Greenbowe J, *et al*: Targeted next generation sequencing identifies markers of response to PD-1 Blockade. Cancer Immunol Res 4: 959-967, 2016.
31. Shao C, Li G, Huang L, Pruitt S, Castellanos E, Frampton G, Carson KR, Snow T, Singal G, Fabrizio D, *et al*: Prevalence of high tumor mutational burden and association with survival in patients with less common solid tumors. JAMA Netw Open 3: e2025109, 2020.
32. Yamada N, Oizumi S, Kikuchi E, Shinagawa N, Konishi-Sakakibara J, Ishimine A, Aoe K, Gemba K, Kishimoto T, Torigoe T and Nishimura M: CD8+ tumor-infiltrating lymphocytes predict favorable prognosis in malignant pleural mesothelioma after resection. Cancer Immunol Immunother 59: 1543-1549, 2010.
33. Anraku M, Cunningham KS, Yun Z, Tsao MS, Zhang L, Keshavjee S, Johnston MR and de Perrot M: Impact of tumor-infiltrating T cells on survival in patients with malignant pleural mesothelioma. J Thorac Cardiovasc Surg 135: 823-829, 2008.
34. Thapa B, Walkeiwicz M, Rivalland G, Murone C, Asadi K, Barnett S, Knight S, Hendry S, Russell P and John T: OA08.05 quantifying tumour infiltrating lymphocytes (TILs) in malignant pleural mesothelioma (MPM)-defining the hot, the warm and the cold tumours. J Thorac Oncol 13: S339, 2018.
35. Galon J, Mlecnik B, Bindea G, Angell HK, Berger A, Lagorce C, Lugli A, Zlobec I, Hartmann A, Bifulco C, *et al*: Towards the introduction of the 'Immunoscore' in the classification of malignant tumours. J Pathol 232: 199-209, 2014.
36. Donnem T, Kilvaer TK, Andersen S, Richardsen E, Paulsen EE, Hald SM, Al-Saad S, Brustugun OT, Helland A, Lund-Iversen M, *et al*: Strategies for clinical implementation of TNM-Immunoscore in resected nonsmall-cell lung cancer. Ann Oncol 27: 225-232, 2016.
37. Hendry S, Salgado R, Gevaert T, Russell PA, John T, Thapa B, Christie M, van de Vijver K, Estrada MV, Gonzalez-Ericsson PI, *et al*: Assessing tumor-infiltrating lymphocytes in solid tumors: A practical review for pathologists and proposal for a standardized method from the International Immunooncology Biomarkers Working Group: Part 1: Assessing the host immune response, TILs in invasive breast carcinoma and ductal carcinoma in situ, metastatic tumor deposits and areas for further research. Adv Anat Pathol 24: 235-251, 2017.
38. Pardoll DM: The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 12: 252-264, 2012.
39. Spranger S, Spaapen RM, Zha Y, Williams J, Meng Y, Ha TT and Gajewski TF: Up-regulation of PD-L1, IDO, and T(regs) in the melanoma tumor microenvironment is driven by CD8(+) T cells. Sci Transl Med 5: 200ra116, 2013.
40. Hegmans JP, Hemmes A, Hammad H, Boon L, Hoogsteden HC and Lambrecht BN: Mesothelioma environment comprises cytokines and T-regulatory cells that suppress immune responses. Eur Respir J 27: 1086-1095, 2006.
41. DeLong P, Carroll RG, Henry AC, Tanaka T, Ahmad S, Leibowitz MS, Sterman DH, June CH, Albelda SM and Vonderheide RH: Regulatory T cells and cytokines in malignant pleural effusions secondary to mesothelioma and carcinoma. Cancer Biol Ther 4: 342-346, 2005.
42. Meloni F, Morosini M, Solari N, Passadore I, Nascimbene C, Novo M, Ferrari M, Cosentino M, Marino F, Pozzi E and Fietta AM: Foxp3 expressing CD4+ CD25+ and CD8+CD28- T regulatory cells in the peripheral blood of patients with lung cancer and pleural mesothelioma. Hum Immunol 67: 1-12, 2006.
43. Kojima M, Kajino K, Momose S, Wali N, Hlaing MT, Han B, Yue L, Abe M, Fujii T, Ikeda K and Hino O: Possible reversibility between epithelioid and sarcomatoid types of mesothelioma is independent of ERC/mesothelin expression. Respir Res 21: 187, 2020.
44. Thiery JP, Acloque H, Huang RY and Nieto MA: Epithelial-mesenchymal transitions in development and disease. Cell 139: 871-890, 2009.
45. Brabletz T, Kalluri R, Nieto MA and Weinberg RA: EMT in cancer. Nat Rev Cancer 18: 128-134, 2018.
46. Aiello NM and Kang Y: Context-dependent EMT programs in cancer metastasis. J Exp Med 216: 1016-1026, 2019.
47. Dongre A and Weinberg RA: New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nat Rev Mol Cell Biol 20: 69-84, 2019.
48. Terry S, Savagner P, Ortiz-Cuaran S, Mahjoubi L, Saintigny P, Thiery JP and Chouaib S: New insights into the role of EMT in tumor immune escape. Mol Oncol 11: 824-846, 2017.
49. Taki M, Abiko K, Ukita M, Murakami R, Yamanoi K, Yamaguchi K, Hamanishi J, Baba T, Matsumura N and Mandai M: Tumor Immune Microenvironment during Epithelial-Mesenchymal Transition. Clin Cancer Res 27: 4669-4679, 2021.
50. Salazar Y, Zheng X, Brunn D, Raifer H, Picard F, Zhang Y, Winter H, Guenther S, Weigert A, Weigmann B, *et al*: Microenvironmental Th9 and Th17 lymphocytes induce metastatic spreading in lung cancer. J Clin Invest 130: 3560-3575, 2020.
51. Blum Y, Meiller C, Quetel L, Elarouci N, Ayadi M, Tashtanbaeva D, Armenoult L, Montagne F, Tranchant R, Renier A, *et al*: Dissecting heterogeneity in malignant pleural mesothelioma through histo-molecular gradients for clinical applications. Nat Commun 10: 1333, 2019.

52. Wu L, Amjad S, Yun H, Mani S and de Perrot M: A panel of emerging EMT genes identified in malignant mesothelioma. Sci Rep 12: 1007, 2022.
53. Raghav K, Liu S, Overman MJ, Willett AF, Knafl M, Fu SC, Malpica A, Prasad S, Royal RE, Scally CP, *et al*: Efficacy, safety, and biomarker analysis of combined PD-L1 (atezolizumab) and VEGF (bevacizumab) blockade in advanced malignant peritoneal mesothelioma. Cancer Discov 11: 2738-2747, 2021.
54. de Reyniès A, Jaurand MC, Renier A, Couchy G, Hysi I, Elarouci N, Galateau-Sallé F, Copin MC, Hofman P, Cazes A, *et al*: Molecular classification of malignant pleural mesothelioma: Identification of a poor prognosis subgroup linked to the epithelial-to-mesenchymal transition. Clin Cancer Res 20: 1323-1334, 2014.
55. Baumann F, Flores E, Napolitano A, Kanodia S, Taioli E, Pass H, Yang H and Carbone M: Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. Carcinogenesis 36: 76-81, 2015.
56. Kaszuba MC, Pulido JS, Folpe AL, Pichurin PN, Goodenberger ML and Spinner RJ: Malignant peripheral nerve sheath tumor in a Patient with BAP1 tumor predisposition syndrome. World Neurosurg 109: 362-364, 2018.
57. Shrestha R, Nabavi N, Lin YY, Mo F, Anderson S, Volik S, Adomat HH, Lin D, Xue H, Dong X, *et al*: BAP1 haploinsufficiency predicts a distinct immunogenic class of malignant peritoneal mesothelioma. Genome Med 11: 8, 2019.
58. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, *et al*: Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21: 2636-2644, 2003.
59. Jänne PA, Wozniak AJ, Belani CP, Keohan ML, Ross HJ, Polikoff JA, Mintzer DM, Taylor L, Ashland J, Ye Z, *et al*: Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: Outcomes of an expanded access program. Clin Lung Cancer 7: 40-46, 2005.
60. Carteni G, Manegold C, Garcia GM, Siena S, Zielinski CC, Amadori D, Liu Y, Blatter J, Visseren-Grul C and Stahel R: Malignant peritoneal mesothelioma-Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agent. Lung Cancer 64: 211-218, 2009.
61. Castagneto B, Botta M, Aitini E, Spigno F, Degiovanni D, Alabiso O, Serra M, Muzio A, Carbone R, Buosi R, *et al*: Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). Ann Oncol 19: 370-373, 2008.
62. Ceresoli GL, Zucali PA, Favaretto AG, Grossi F, Bidoli P, Del Conte G, Ceribelli A, Bearz A, Morenghi E, Cavina R, *et al*: Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. J Clin Oncol 24: 1443-1448, 2006.
63. Santoro A, O'Brien ME, Stahel RA, Nackaerts K, Baas P, Karthaus M, Eberhardt W, Paz-Ares L, Sundstrom S, Liu Y, *et al*: Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaïve patients with malignant pleural mesothelioma: Results of the International Expanded Access Program. J Thorac Oncol 3: 756-763, 2008.
64. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, Molinier O, Corre R, Monnet I, Gounant V, *et al*: Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): A randomised, controlled, open-label, phase 3 trial. Lancet 387: 1405-1414, 2016.
65. Hassan R, Thomas A, Nemunaitis JJ, Patel MR, Bennouna J, Chen FL, Delord JP, Dowlati A, Kochuparambil ST, Taylor MH, *et al*: Efficacy and safety of avelumab treatment in patients with advanced unresectable mesothelioma: Phase 1b results from the JAVELIN solid tumor trial. JAMA Oncol 5: 351-357, 2019.
66. Fennell DA, Ewings S, Ottensmeier C, Califano R, Hanna GG, Hill K, Danson S, Steele N, Nye M, Johnson L, *et al*: Nivolumab versus placebo in patients with relapsed malignant mesothelioma (CONFIRM): A multicentre, double-blind, randomised, phase 3 trial. Lancet Oncol 22: 1530-1540, 2021.
67. Popat S, Curioni-Fontecedro A, Dafni U, Shah R, O'Brien M, Pope A, Fisher P, Spicer J, Roy A, Gilligan D, *et al*: A multicentre randomised phase III trial comparing pembrolizumab versus single-agent chemotherapy for advanced pre-treated malignant pleural mesothelioma: The European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial. Ann Oncol 31: 1734-1745, 2020.
68. Maio M, Scherpereel A, Calabrò L, Aerts J, Perez SC, Bearz A, Nackaerts K, Fennell DA, Kowalski D, Tsao AS, *et al*: Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): A multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. Lancet Oncol 18: 1261-1273, 2017.
69. Desai A, Karrison T, Rose B, Pemberton E, Hill B, Straus CM, Tan Y-HC, Seiwert TY and Kindler HL: Phase II trial of pembrolizumab (P) in patients (pts) with previously-treated mesothelioma (MM). J Clin Oncol 36 (Suppl 15): S8565, 2018.
70. Marmarelis ME, Wang X, Roshkovan L, Walker S, McNulty S, Ciunci CA, Muira J, Katz SI, Cengel KA, *et al*: Real-world outcomes of pembrolizumab in peritoneal mesothelioma. J Clin Oncol 38 (Suppl 15): e21094, 2020.
71. Peters S, Scherpereel A, Cornelissen R, Oulkhouir Y, Greillier L, Kaplan MA, Talbot T, Monnet I, Hiret S, Baas P, *et al*: First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743. Ann Oncol 33: 488-499, 2022.
72. Calabrò L, Rossi G, Morra A, Rosati C, Cutaia O, Daffinà MG, Altomonte M, Di Giacomo AM, Casula M, Fazio C, *et al*: Tremelimumab plus durvalumab retreatment and 4-year outcomes in patients with mesothelioma: A follow-up of the open label, non-randomised, phase 2 NIBIT-MESO-1 study. Lancet Respir Med 9: 969-976, 2021.
73. Calabrò L, Morra A, Giannarelli D, Amato G, D'Incecco A, Covre A, Lewis A, Rebelatto MC, Danielli R, Altomonte M, *et al*: Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): An open-label, non-randomised, phase 2 study. Lancet Respir Med 6: 451-460, 2018.
74. Raghav K, Liu S, Overman M, Morani A, Willette A, Fournier K and Varadhachary G: Clinical efficacy of immune checkpoint inhibitors in patients with advanced malignant peritoneal mesothelioma. JAMA Netw Open 4: e2119934, 2021.
75. Forde PM, Anagnostou V, Sun Z, Dahlberg SE, Kindler HL, Niknafs N, Purcell T, Santana-Davila R, Dudek AZ, Borghaei H, *et al*: Durvalumab with platinum-pemetrexed for unresectable pleural mesothelioma: Survival, genomic and immunologic analyses from the phase 2 PrE0505 trial. Nat Med 27: 1910-1920, 2021.
76. Foote MB, Shia J, Zauderer MG, Nash GM and Cercek A: Treatment of platinum nonresponsive metastatic malignant peritoneal mesothelioma with combination chemoimmunotherapy. J Immunother 45: 100-103, 2022.
77. Scagliotti GV, Gaafar R, Nowak AK, Nakano T, van Meerbeeck J, Popat S, Vogelzang NJ, Grosso F, Aboelhassan R, Jakopovic M, *et al*: Nintedanib in combination with pemetrexed and cisplatin for chemotherapy-naive patients with advanced malignant pleural mesothelioma (LUME-Meso): A double-blind, randomised, placebo-controlled phase 3 trial. Lancet Respir Med 7: 569-580, 2019.
78. Bijelic L, Darcy K, Stodghill J, Tian C and Cannon T: Predictors and outcomes of surgery in peritoneal mesothelioma: An analysis of 2000 patients from the National cancer database. Ann Surg Oncol 27: 2974-2982, 2020.
79. Thompson JC, Hwang WT, Davis C, Deshpande C, Jeffries S, Rajpurohit Y, Krishna V, Smirnov D, Verona R, Lorenzi MV, *et al*: Gene signatures of tumor inflammation and epithelial-to-mesenchymal transition (EMT) predict responses to immune checkpoint blockade in lung cancer with high accuracy. Lung Cancer 139: 1-8, 2020.
80. de Boer NL, van Kooten JP, Burger JWA, Verhoef C, Aerts JGJV and Madsen EVE: Adjuvant dendritic cell based immunotherapy (DCBI) after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal mesothelioma, a phase II single centre open-label clinical trial: Rationale and design of the MESOPEC trial. BMJ Open 9: e026779, 2019.
81. Adusumilli PS, Zauderer MG, Rivière I, Solomon SB, Rusch VW, O'Cearbhaill RE, Zhu A, Cheema W, Chintala NK, Halton E, *et al*: A Phase I Trial of Regional Mesothelin-Targeted CAR T-cell therapy in patients with malignant pleural disease, in combination with the Anti-PD-1 Agent Pembrolizumab. Cancer Discov 11: 2748-2763, 2021.