Biomarkers to predict the benefits of immune-checkpoint blockade-based therapy in patients with malignant peritoneal mesothelioma (Review)

CHUNHONG WANG, YAN ZHAO and WANRU LIANG

Department of Hematology and Oncology, The Second Hospital of Jilin University, Changchun, Jilin 130000, P.R. China

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Abstract. Malignant peritoneal mesothelioma (MPeM) is a type of rare and highly lethal tumor. Immune checkpoint blockade (ICB)-based therapy has shown encouraging clinical activity for MPeM. However, no definitive biomarkers have been identified for predicting which patients with MPeM will benefit from ICB-based therapy. At present, there are several novel potential biomarkers proposed for predicting the response to ICB-based therapy, and biomarkers available in MPeM cells and in the tumor microenvironment have been identified with the potential to predict the efficacy of ICB-based therapy in MPeM. According to the molecular characteristics of MPeM itself, the feasibility of biomarkers in practice, and the body of available evidence, we hypothesize that the following five types of biomarkers can be used to predict the response of ICB-based therapy in patients with MPeM: Tertiary lymphoid structures, immune checkpoints and their ligands, fusion gene neoantigen burden, *BRCA1*-associated protein-1 haploinsufficiency and transcriptome-based biomarkers. The present review discusses the value and limitations of each type of biomarker, and potential solutions to address the limitations are proposed. The aim of the present review is to provide a background for future studies on ICB-based therapy for MPeM.

Contents

Correspondence to: Dr Chunhong Wang, Department of Hematology and Oncology, The Second Hospital of Jilin University, 4026 Yatai Street, Nanguan, Changchun, Jilin 130000, P.R. China
E-mail: wang_ch@jlu.edu.cn

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1. Introduction

Malignant peritoneal mesothelioma (MPeM) is a rare and highly lethal type of cancer. Approximately 500 to 700 new cases are diagnosed annually in the United States and median overall survival (OS) is 6 months to 1 year. Platinum + pemetrexed with or without bevacizumab is the standard first-line therapy for patients with advanced disease; however, its efficacy is limited (1,2).

Immune checkpoint blockade (ICB)-based therapy has revolutionized the treatment of several types of solid tumors. Currently, approved ICB treatments worldwide include anti-programmed death-1 (PD-1)/anti-programmed death-ligand 1 (PD-L1), anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and anti-lymphocyte activation gene-3 (LAG-3) treatment (3). Given the promising results reported for malignant pleural mesothelioma (MPM), certain small studies have focused on the efficacy of ICB-based therapy for MPeM (4-6). In a real-world study, 29 patients with MPeM were treated with nivolumab + ipilimumab or a single immune checkpoint inhibitor as the second-line treatment (7). The objective response rate (ORR) was 19.2% (5/26; 95% CI, 6.6-39.4). In a phase II single-center study (8), 20 patients with MPeM were treated with atezolizumab + bevacizumab as the second-line treatment and the ORR was 40% (8/20; 95% CI 19.1-64.0). Both studies demonstrated the encouraging clinical activity of ICB treatment for MPeM.

However, it is evident that only a subset of patients with MPeM may benefit from ICB-based therapy. Identifying patients who may benefit from ICB-based therapy is a subject of research. To date, tumor mutation burden (TMB), expression of PD-L1 and microsatellite instability (MSI) are the three biomarkers validated for predicting the response to ICB; however, there is no widely accepted method for prediction based on biomarkers, and their applications vary by disease site (9-11). Certain patients with TMB-low and PD-L1 negative tumors also exhibit marked treatment responses; meanwhile, other patients with MSI-high tumors show primary or secondary resistance to ICB therapy (12,13). Other biomarkers, including the tumor microenvironment (TME) and the components in the TME, host immune response patterns based on transcriptomic and proteomic analysis, as well as specific mutations (such as gene fusions) or clonal mutations, are currently being explored. Malignant mesothelioma has been

traditionally assumed to be a TMB-low tumor with extremely low MSI prevalence (14,15). Therefore, there is an urgent need to develop appropriate biomarkers for predicting the efficacy of ICB-based therapy (including, but not limited to, anti-PD-1/anti-PD-L1 treatment) for patients with MPeM. The present review focuses on five types of promising biomarkers currently available, highlighting evidence that supports the predictive role of these biomarkers for ICB-based therapy for MPeM (Fig. 1 and Table I). Additionally, the limitations of each type of biomarker are discussed and possible methods for addressing these problems are mentioned.

2. Tertiary lymphoid structures (TLS)

It is well established that the TME is a complex system. It includes multiple cellular and non-cellular components and serves an important role in several stages of tumor development and progression, including metastasis, and evasion of immune monitoring and treatment. Initially, the majority of tumor immunology research focused on how the function and relative abundance of T cells and macrophages within the TME mediated effector responses (16-19). Recently, it was reported that other tumor-infiltrating immune subsets, such as B cells and mast cells, were essential for effector responses (20,21).

TLS are organized aggregates of immune cells, characterized by an inner zone of CD20+ B cells surrounded by CD3+ T cells. In addition to B and T cell populations, TLS are also populated by dendritic cells (DC), macrophages and other immune cell types (22-24). Several studies have reported that TLS were detectable in certain types of tumors, such as cutaneous angiosarcoma, colorectal cancer, hepatocellular carcinoma, gastric cancer, gastrointestinal stromal tumor, breast cancer and lung squamous cell carcinoma (25-31). However, studies focusing on TLS in MPeMs are limited. In a study published in 2005, it was reported that there was a large degree of infiltration of lymphocytes and plasma cells, including lymphoid aggregates and follicles within the omental fat or omental fibrous tissue surrounding the areas of an invading tumor in 13/75 female patients with MPeM (32). This morphological change is akin to a TLS. Recently, Benzerdjeb *et al* (33) reported there were numerous lymphoid aggregates with or without germinal centers in 52/138 cases with epithelioid MPeM. Another study demonstrated that TLS were present in MPeMs (32). Additionally, the study reported that neoadjuvant chemotherapy could induce the formation of TLS; however, the study did not report on the relationship between the presence of TLS and the response to ICB therapy.

TLS are an important component of the TME and serve a critical role in regulating tumor-specific immune responses (24,32). A growing body of evidence has suggested that TLS can serve as a predictive biomarker for the response to ICB treatment in certain types of solid tumors. The presence of TLS in pre-treatment biopsies of melanoma, renal cell carcinoma, soft tissue sarcoma and urothelial carcinoma has been reported to be associated with the response to anti-PD-1 or anti-PD-1 + anti-CTLA-4 treatment (20,24,34-36). These studies highlighted that there was a higher density of TLS in pre-treatment tumor tissues of responder patients as compared to non-responder patients. Furthermore, in a randomized phase II study, patients with MPM were treated using a single cycle of durvalumab + tremelimumab or durvalumab alone in a neoadjuvant setting (37). There was a marked increase in TLS density following ICB combination therapy, a greater increase in TLS formation in tumors that had partial remission (PR), and a higher pre-treatment TLS density associated with PR. The study also reported that pre-treatment TLS was more closely associated with the efficacy of ICB treatment, and TLS formation could be induced following ICB treatment just as with chemotherapy (33,37). This evidence suggests that pre-treatment TLS may fully represent the initial tumor status and have a greater impact on the response to ICB therapy. Thus, the presence of TLS pre-treatment is more accurate in predicting the response to ICB treatment, as it implicates that the tumor and the host under the influence of the tumor may already be generating an antitumor immune response, which is potentially enhanced by ICB therapy and chemotherapy.

The findings from the limited body of studies indicate that TLS are present in MPeM and the presence of TLS pre-treatment has potential as a biomarker for predicting the efficacy of ICB therapy. Notably, TLS is a readily testable and acquirable indicator using immunohistochemistry in the clinic (23). However, there are no studies on the predictive role of TLS for ICB treatment in MPeM, to the best of our knowledge. Additionally, the underlying mechanism of TLS formation is not clear, and this may be critical for understanding the predictive value of TLS status in determining the efficacy of ICB therapy. Therefore, additional studies are required to verify the relationship between the TLS and ICB treatment in MPeM.

3. Immune checkpoints and their ligands

PD-L1. PD-L1 expression is the most commonly used biomarker for predicting the benefits of anti-PD-1/anti-PD-L1 treatment, and it has been reported that PD-L1 is expressed in mesotheliomas (38-40). A study by Chapel *et al* (38) used Dako PD-L1 IHC 22C3 pharmDx and Dako PD-L1 IHC 28-8 pharmDx (Agilent Technologies, Inc.) to detect PD-L1 expression in mesothelioma, with a 22 and 27% positive tumor proportion score (TPS; cutoff ≥1%), respectively. The proportion of cases with positive PD-L1 expression was notably higher among MPeMs compared with that in MPMs (22C3 assay: MPM, 18% and MPeM 54%; 28-8 assay: MPM, 24% and MPeM, 54%). In another study, the positive combined positive score (CPS) and positive TPS (both cutoff ≥1%; 22C3 assay) were 76 and 43% among MPeMs, respectively (39). More aggressive biphasic/sarcomatoid MPeMs had a higher CPS and TPS. However, a study by Pezzuto *et al* (40) reported that there were only 2% positive TPS (cutoff ≥1%; 22C3 assay) cases among 43 patients with MPeM. It was hypothesized that this discrepancy was attributed to the small sample size of non-epithelioid cases, which are more commonly positive for PD-L1.

The role of PD-L1 in predicting the response to ICB-based therapy for MPeM is also contested. In a phase II trial, 56 patients with MPM and eight patients with MPeM were treated with pembrolizumab alone (41). The ORR was 20 and 12.5%, respectively. Notably, PD-L1 expression was not associated with ORR. Moreover, Raghav *et al* (8) reported 20 patients with MPeM treated with atezolizumab + bevacizumab. The ORR was 40% and responses were reported in both

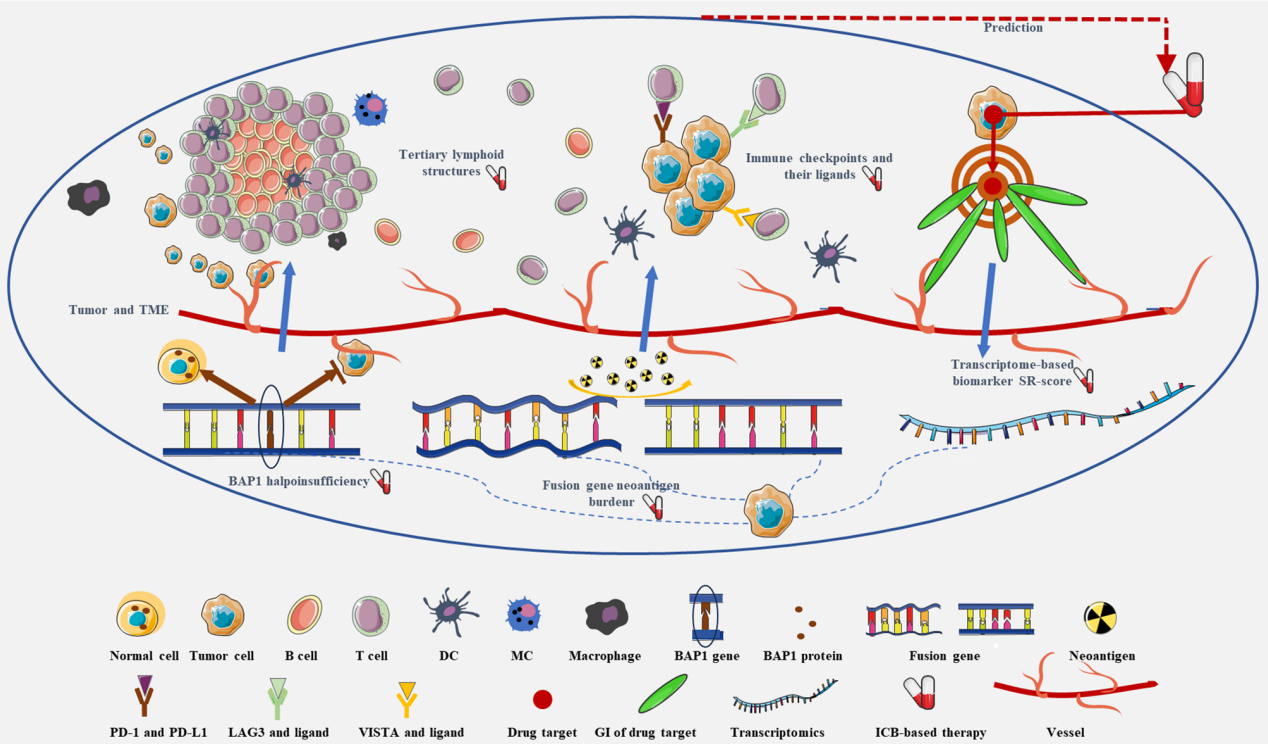

Figure 1. Model of the five types of predictive biomarkers for immune checkpoint blockade-based therapy in patients with malignant peritoneal mesothelioma, produced using Servier Medical Art [Les Laboratoires Servier (SAS); (https://smart.servier.com)]. TME, tumor microenvironment; BAP1, *BRCA1*-associated protein-1; SR, synthetic rescue; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; LAG3, anti-lymphocyte activation gene-3; VISTA, V-domain Ig suppressor of T cell activation; DC, dendritic cell; MC, mast cell; ICB, immune-checkpoint blockade; GI, genetic interaction.

PD-L1-positive and -negative cases. Given these contradictory results, there is no consensus on identifying patients with MPeM who would benefit from anti-PD-1/anti-PD-L1 treatment based solely on PD-L1 expression. Therefore, there is no solid evidence to support PD-L1 expression as a biomarker for predicting the efficacy of anti-PD-1/anti-PD-L1 treatment for MPeM. It is necessary to determine PD-L1 expression status and the association between PD-L1 expression and the efficacy of anti-PD-1/anti-PD-L1 treatment in patients with MPeM. Additionally, there is a need to optimize other histological and molecular characteristics as biomarkers to guide ICB-based therapy for MPeM.

V-domain Ig suppressor of T cell activation (VISTA). VISTA is a negative checkpoint regulator, which is expressed in most hematopoietic cells. In addition, VISTA is expressed in numerous types of tumor cells (42-45). Several studies have reported notable upregulated expression of VISTA in immunohistochemical analysis of malignant mesothelioma tissues and in the normal mesothelium, as well as higher VISTA expression levels in the epithelioid subtype (46-50).

Chung *et al* (49) reported no significant difference in VISTA expression between MPMs and MPeMs using immunohistochemistry. However, Offin *et al* (50) reported that, in 50 patients with MPeM, up to 89% exhibited positive VISTA expression. In addition, two studies reported that anti-PD-1 and anti-CTLA-4 treatment resulted in upregulated VISTA expression in the TME, resulting in no benefit from or resistance to anti-PD-1 and anti-CTLA-4 treatment (51,52). Gao *et al* (51) evaluated the expression of PD-L1 and VISTA using immunohistochemistry in the tumors of pre- and post-treatment patients with prostate cancer who did not benefit from ipilimumab treatment. They found increased PD-L1 and VISTA expression and a higher frequency of upregulated VISTA expression in dependent subsets of T cells and macrophages in the samples of post-ipilimumab treatment. They hypothesized that VISTA was a compensatory inhibitory pathway following ipilimumab treatment. Kakavand *et al* (52) reported that 8/12 patients with melanoma with acquired resistance to anti-PD-1 treatment had a notably increased frequency of VISTA-positive lymphocytes. They hypothesized that VISTA represented an important mechanism of acquired resistance in patients with melanoma treated with anti-PD-1 treatment. These outcomes suggest that VISTA expression in MPeMs may be involved in a mechanism that underlies the inefficacy of anti-PD-1 and anti-CTLA-4 treatment. Thus, ICB treatment targeting VISTA may be a potential therapeutic strategy for the management of MPeM, particularly in patients with an epithelioid subtype (53,54).

VISTA serves a role in regulating the steady state of both lymphoid and myeloid cells involved in the immune system (53-56). Liu *et al* (57) reported that VISTA/PD-1 double deficient knockout (KO) mice exhibited notably higher levels of chronic inflammation and activation of T cells than the single KO mice. This suggests that VISTA had a nonredundant role, distinct from the PD-1/PD-L1 pathway. Moreover, an *ex vivo* study supported the aforementioned result, in which pro-inflammatory factors were upregulated and anti-inflammatory factors were downregulated when T cells were co-cultured with MCF7 cells with VISTA and

Table I. Promising biomarkers for predicting the efficacy of immune-checkpoint blockade-based therapy for malignant peritoneal mesothelioma.

Biomarker	Comments	(Refs.)
Immune checkpoints and their ligands (PD-L1, VISTA and LAG-3)	Encouraging efficacy has been reported for blockade of PD-1/PD-L1, LAG-3 and VISTA. PD-L1 combined with VISTA or LAG-3 has been reported to exhibit better predictive value for ICB-based therapy.	(5,6,57-61,63,66-69)
TLS	TLS is an easily testable indicator using immunohistochemistry. The underlying mechanism of TLS formation may be more important when using TLS to predict the efficacy of ICB-based therapy.	(23,32,33,37)
Fusion gene neoantigen burden	Fusion gene neoantigen burden has greater potential than the tumor mutation burden in predicting the response to ICB-based therapy for MPeM, particularly when antigen processing and presentation are taken into account.	(77-79,83,91,92)
BAP1 haploinsufficiency	BAP1 inactivation is one of the driver events of malignant mesothelioma. BAP1 haploinsufficiency may be specific for MPeM in guiding ICB-based therapy. BAP1 haploinsufficiency-based biomarkers, such as the BAP1-score, may be superior to BAP1 haploinsufficiency alone.	(64,65,95,98)
Transcriptome-based biomarkers	It is more complicated to detect transcriptome-based biomarkers; however, they may provide valuable information in guiding ICB-based therapy.	(103,104,106)

ICB, immune-checkpoint blockade; MPeM, malignant peritoneal mesothelioma; TLS, tertiary lymphoid structures; PD-1, programmed death-1; VISTA, V-domain Ig suppressor of T cell activation; LAG-3, anti-lymphocyte activation gene-3; BAP1, *BRCA1*-associated protein-1.

CTLA-4 expression knocked down. Combined knockdown of VISTA and CTLA-4 inhibited MCF7 breast cancer cell development (58). In a study of liver cancer using a mouse model, symptoms and tumor growth were reduced using anti-VISTA monoclonal antibodies (mAbs), resulting in a reduction in mouse mortality (59). In the study of CT26 colon cancer cells and less immunogenic B16BL6 melanoma mice models, the combinatorial treatment of VISTA and PD-L1 mAbs led to suppressed tumor growth and tumor regression and conferred a survival advantage compared with VISTA mAb alone or PD-L1 mAb alone, respectively (57). Treatment with the anti-VISTA antibody KVA12123 mediated strong antitumor activity and showed enhanced efficacy in combination with anti-PD-1 treatment in several tumor models, including bladder cancer, colon cancer, lymphoma and melanoma (60). These results suggest that anti-VISTA treatment with anti-PD-1/PD-L1 or anti-CTLA-4 treatment may contribute to the acquisition of an immuno-active TME, enhancing antitumor responses and improving efficacy.

Given the high frequency of upregulated VISTA expression in MPeM and the marked benefits from VISTA blockade treatment in preclinical models, VISTA blockade, particularly combined with anti-PD-1/PD-L1 or anti-CTLA-4 treatment, is a promising approach for management of MPeM. The small molecule immune checkpoint inhibitor CA-170, which targets both PD-L1 and VISTA, has been reported to exhibit antitumor efficacy preclinically (61). There is currently an ongoing phase I study in which patients with tumors with high levels of VISTA expression, including malignant mesothelioma, are being treated with CA-170 (62). Therefore VISTA, particularly when combined with PD-L1, may serve as a suitable biomarker and therapeutic target to improve the outcomes in patients receiving anti-PD-1/PD-L1 or anti-CTLA-4 treatment.

LAG-3. In addition to PD-L1 and VISTA, LAG-3 may also serve as a potential biomarker for guiding ICB-based therapy for MPeM. LAG-3 is expressed on the membranes of immune cells, including T cells, and it negatively regulates T-cell proliferation and effector T-cell function (63). Upregulated LAG-3 mRNA expression was detected in malignant mesothelioma under specific settings. In a comprehensive analysis of 19 cases of treatment-naive MPeM in 18 patients, high levels of LAG-3 mRNA expression were detected in MPeM with *BRCA1*-associated protein-1 (BAP1) haploinsufficiency (64). In another analysis of MPM datasets from The Cancer Genome Atlas (TCGA; n=86) and Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (n=61), the mRNA expression levels of LAG-3 and VISTA were markedly higher in patients with tumors with BAP1 mutations [not accompanied with neurofibromatosis type 2 (NF2) and cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) mutations] than tumors with NF2 or CDKN2A/B mutation alone, or BAP1 accompanied with NF2 and CDKN2A/B mutations (65).

Preclinical experiments have indicated that LAG-3 and PD-1 may have a synergistic effect in inhibiting T-cell activation and promoting tumor immune evasion. Simultaneous blockade of both receptors has a more potent immune response compared with blocking either receptor alone (66,67). In the

AB1-HA BALB/cJ mesothelioma mice model, a delay in tumor growth and a notable improvement in survival were observed for anti-PD-L1 and anti-PD-L1 + anti-LAG-3 treatment when compared with the PBS control group. The combination of PD-L1 and LAG-3 blockade differed more from the PBS control than the anti-PD-L1 monotherapy, suggesting that anti-LAG-3 treatment had an additional effect (68). Notably, anti-LAG-3-based treatment has been used in the clinic. The US Food and Drug Administration approved the combination of relatlimab (anti-LAG-3 mAb) and nivolumab (anti-PD-1 mAb) for the treatment of unresectable or metastatic melanoma in 2022 (69). The approval was based on a phase II/III randomized trial, in which treatment with relatlimab + nivolumab was associated with a 47.7% 12-month progression-free survival (PFS) in patients with melanoma, compared with 36% in those who underwent nivolumab monotherapy. In a prespecified exploratory analysis, median PFS estimates were markedly longer for patients with a LAG-3 expression of ≥1% than those with a LAG-3 expression of <1% (63).

Similar to VISTA, LAG-3 blockade, particularly when combined with anti-PD-1/PD-L1 treatment, is promising for MPeM. Therefore LAG-3, particularly when combined with PD-L1, may serve as a biomarker to guide the blockade of VISTA + PD-1 treatment. Additionally, it is common that drugs approved for common tumors are also used to treat rarer tumors clinically (70-72). The potential use of relatlimab provides a potential opportunity for the treatment of MPeM.

4. Fusion gene neoantigen burden

Neoantigens are tumor-specific antigens that can stimulate an antitumor immune response (73). An increasing number of studies have reported that high clonal neoantigen burden (present in all tumor cells) and low neoantigen intratumor heterogeneity are associated with the efficacy of ICB treatment (73-76). Previously, it was hypothesized that single-nucleotide variants (SNVs) and insertions or deletions (indels) were the most common source of tumor neoantigen acquisition. At present, gene fusions are also suggested to be a notable means of acquisition of tumor neoantigens with higher immunogenic potential (77-79). Analysis of whole genomes from 2,528 tumors revealed that gene fusions from genomic rearrangement notably contributed to neoantigen formation in both quantity and quality (77). By comparing TCGA fusion candidate neoantigens with TCGA SNVs and indel candidate neoantigens, it was reported that gene fusions generated six-fold more candidate neoantigens and 11-fold more specific candidate neoantigens (78).

Chromosomal rearrangements are the source of gene fusions and they are common in malignant mesotheliomas (80-83). Yoshikawa *et al* (84) reported multiple noncontiguous minute deletions on chromosome 3p21 in malignant mesotheliomas, where the *BAP1* gene is located. This genetic change was attributed to chromothripsis, which is a mutational phenomenon in which the rapid accrual of hundreds of rearrangements occurs (80). Oey *et al* (81) reported that 8/9 tested mesotheliomas had complex rearranged genomes with evidence of chromothripsis and chromoplexy, the latter representing a series of linked translocations or weaving of chromosomal fragments (80). In the study by Bueno *et al* (82), gene fusions from chromosomal rearrangements and splice alterations were frequent mechanisms for the inactivation of the driver genes of malignant mesothelioma, such as *NF2*, *BAP1* and *SET domain containing 2*. Neoantigen prediction analysis revealed that neoantigens formed from gene fusions. Mansfield *et al* (83) reported that there were 1,535 chromosomal rearrangements by Mate-pair sequencing in 22 treatment-naive cases of malignant mesothelioma specimens and several of these abnormalities were obtained due to chromothripsis and chromoplexy. The study also demonstrated that gene fusions from chromosomal rearrangements could result in neoantigen formation. Together, these results demonstrated that chromosomal rearrangements were common in malignant mesotheliomas, in accordance with the complex structural and numerical abnormalities of the karyotype reported in other studies (85,86). Malignant mesotheliomas may exhibit marked neoantigen formation from rearrangement-related gene fusions. However, chromosomal rearrangements and rearrangement-related gene fusions were notably underestimated due to the limitations of previous detection techniques and approaches, such as standard next-generation sequencing technology (80,82).

Fusion gene neoantigens tend to have higher immunogenic potential and trigger more effective adaptive immune responses. Analysis of whole genomes from 2,528 tumors observed the derived neoantigens from genomic rearrangements, especially the clonal neoantigens, were extensively immuno-edited, which suggested their immunogenic potential (77). A comprehensive analysis of tumor neoantigens reported that candidate neoantigens with the highest immunogenic potential were produced by fusion genes in 32.2% of cases in a TCGA dataset (78). By analyzing 522 cases of head and neck squamous cell carcinoma with a low TMB, it was reported that fusion-associated neoantigens were able to stimulate a more potent T cell response compared with missense mutation-associated neoantigens (79). Fusion gene neoantigens with the immunogenic potential to elicit an adaptive immune response were also observed in mesothelioma. Mansfield *et al* (83) estimated that 1,535 chromosomal rearrangements in malignant mesothelioma specimens resulted in the expression of 179 novel peptides. A number of the 179 candidate neoantigens could bind to patient-specific human leukocyte antigen molecules and improve the expansion of tumor-infiltrating T cells in the TME (83). These results revealed that neoantigens from chromosomal rearrangement-related gene fusions in malignant mesotheliomas had the potential to elicit more effective anti-neoplasm immune responses.

Conventionally, TMB is used to estimate the neoantigen burden and has been shown to predict the efficacy of anti-PD-1/anti-PD-L1 treatment for several tumors (87-90). However, malignant mesotheliomas, including MPeM, are commonly viewed as tumors with a low TMB. This is attributed to the disadvantages of conventional detection techniques and approaches (84). Notably, Kosari *et al* (91) used the burden of tumor junction from chromosomal rearrangements as a surrogate biomarker for determining the fusion gene neoantigen burden. It was reported that tumor junction burden was associated with improved survival outcomes in patients with mesothelioma treated with ICB in the presence of antigen

processing and presentation gene set expression. Moreover, it was revealed that antigen processing and presentation were essential for the role of tumor junction burden. Another study also emphasized that a high burden of neopeptides could successfully predict the response to PD-1 inhibitors in patients with advanced MPM or melanoma when accompanied by upregulated expression of major histocompatibility complex proteins specific for the neopeptides (92). These studies suggest that fusion gene neoantigen burden could be used instead of TMB and that it serves a predictive role in ICB treatment in mesothelioma when antigen processing and presentation are taken into account.

Together, the available studies suggest that malignant mesotheliomas exhibit a higher degree of neoantigen formation, and this can be attributed to chromosomal rearrangement-related gene fusions. When neoantigens are processed and presented appropriately, they have a notable immunogenic potential to affect effector cells in the TME, and the burden of these neoantigens has potential as a biomarker for predicting the response to ICB treatment for patients with MPeM. However, prospective studies are required to validate these findings.

5. BAP1 haploinsufficiency

BAP1 is a tumor suppressor gene and *BAP1* inactivation is a key driver event in malignant mesotheliomas. In a single-center study including 244 cases with MPeM, 55% of the cases were BAP1-negative based on immunohistochemistry analysis (93). In another study, loss of BAP1 nuclear expression and *BAP1* heterozygous inactivation was observed in 57 and 13%, respectively, of the 46 cases with MPeM (94). These studies demonstrate that loss of BAP1 function is common in MPeM.

Shrestha *et al* (64) performed integrative multi-omics analyses and reported that BAP1 haploinsufficiency [homozygous or heterozygous loss of *BAP1* (*BAP1*^{del})] resulted in a distinct molecular subtype of MPeM with strong cytokine signaling activity and innate immune system activity. Further analysis demonstrated that there was increased infiltration of T cells in the TME of *BAP1*^{del} MPeM. Additionally, the mRNA expression levels of immune checkpoint receptors (such as PD-1, CD80, CTLA-4, LAG-3 and inducible co-stimulator) were increased in *BAP1*^{del} MPeM. The aforementioned signature of *BAP1*^{del} MPeM was also reported in certain other solid tumors. In a comprehensive analysis of data of MPM, the tumors with alterations in only *BAP1* (not accompanied by *NF2* or *CDKN2A/B* mutations) had a distinct expression of inflammatory microenvironment genes, including the activation of interferon signaling and interferon regulatory factor (IRF) transcription factors. The mRNA expression levels of the immune checkpoint receptors LAG-3 and VISTA, were also upregulated (65). In two independent uveal melanoma cohorts, the lack of BAP1 expression detected using immunohistochemistry was associated with increased T cell infiltration into the TME (95). The inflammatory TME formation in *BAP1*^{del} MPeMs could be due to the fact that the majority of *BAP1* mutations in MPeM are frameshift indels and chromosomal rearrangements, both of which are associated with neoantigen formation (77,79,96). Furthermore, as previously discussed, tumor neoantigens are critical for T cell expansion and activation. Additionally, BAP1-inactivation notably increases IRF8 activity, which is involved in DC differentiation. DCs with antigen-presenting function are highly effective at stimulating cytotoxic T cells in the TME (46). These outcomes suggest that insufficient BAP1 function is associated with the formation of an inflammatory TME in MPeM. Additionally, negative immune checkpoint receptors beyond PD-1 are highly expressed, including LAG-3 and VISTA (64,65).

Based on the aforementioned findings, it is reasonable to treat *BAP1*^{del} MPeM with ICB-based therapy, such as anti-PD-1/anti-PD-L1, anti-LAG-3 and anti-VISTA treatment. BAP1 haploinsufficiency may serve as a biomarker for predicting the response to ICB therapy. In a case report, a patient with MPeM with loss of nuclear expression of BAP1 was treated with nivolumab + ipilimumab as the first-line therapy, and they achieved PR after 8 months (97). There is BAP1 inactivation in 70% of patients with MPeM (57% loss of BAP1 nuclear expression and 13% *BAP1* heterozygous inactivation), but only 19% of patients benefit from anti-PD-1/anti-PD-L1 treatment alone and 40% of patients benefit from anti-PD-1/anti-PD-L1 + anti-CTLA-4 and anti-PD-1/anti-PD-L1 + anti-angiogenesis treatment as ≥second-line therapy (7,8,94). It is unclear whether the response rate may be higher when ICB-based therapy is used as a first-line therapy, or when patients are treated with anti-PD-1/anti-PD-L1 + anti-CTLA-4, anti-LAG-3 or anti-VISTA treatment.

Therefore, BAP1 haploinsufficiency alone may not be adequate for predicting the response to ICB-based therapy. In a retrospective analysis of the JAVELIN Renal 101 and checkmate-009/010/025 trials, the BAP1 score was developed using the top 20 BAP1 mutation-associated differentially expressed genes. The BAP1-score was a significant predictor of the immune microenvironment and the clinical benefits of ICB-based therapies in patients with advanced clear cell renal cell carcinoma (98). Therefore, BAP1 haploinsufficiency-based biomarkers may be superior to BAP1 haploinsufficiency alone. The value of BAP1 haploinsufficiency or BAP1 haploinsufficiency-based biomarkers both warrant further investigation.

6. Transcriptome-based biomarkers

It has been reported that certain tumor transcriptomic changes can be used as biomarkers to guide tumor therapy (99-102). However, the predictive roles of these biomarkers are limited to a highly specific clinical context and treatments. Lee *et al* (103) developed a uniform systematic approach, SynthEtic LEthality and rescue-mediated precision onCology via the Transcriptome (SELECT), which does not train any model parameters by looking at the test data. Using SELECT, the best drug was selected for a given patient based on the tumor pre-treatment transcriptome data. Unlike commonly matching drugs based on the transcriptome-based expression of their targets, SELECT focused on identifying and utilizing the genetic interaction (GI) of drug targets as the biologically testable biomarkers for the prediction of a therapeutic response. The study analyzed data obtained from TCGA and found notable pan-cancer synthetic rescue (SR) interaction partners of PD-1/PD-L1 and CTLA-4. SR interaction is described as the inactivation of one gene reducing cell viability, but the alteration of another gene's activity-rescuing viability. The study defined SR scores, where

tumors with higher SR scores were predicted to respond better to ICB treatment (anti-PD-1/anti-PD-L1 and anti-CTLA-4 treatment). Higher SR scores were associated with better responses to ICB treatment based on an analysis of 21 immune checkpoint therapy datasets. Subsequently, Nair *et al* (104) used the same parameters and procedure described by Lee *et al* (103) to predict the response to anti-PD-1 treatment in an National Cancer Institute mesothelioma patient cohort, which included an equal proportion of patients with pleural and peritoneal mesothelioma. SR scores were able to accurately predict the response to anti-PD-1 treatment in these patients with mesothelioma.

ENLIGHT was designed and developed on the basis of SELECT, which is a transcriptomics-based computational approach that identifes clinically relevant genetic interactions and uses them to predict responses to a variety of therapies in multiple cancer types. ENLIGHT-matching scores (EMS) could be used to predict the efficacy of immunotherapies (including ICBs and mAbs) more accurately than targeted small molecules. EMS was comparable with other ICB-specific biomarkers, including the proliferation signature, cytolytic index and interferon (IFN)-γ signature. The combination of EMS and IFN-γ was more accurate than either of them alone or the other combinations in the ICB cohorts (105). Similar to SELECT, ENLIGHT did not require training on previous treatment response data, which is useful for rare tumors, such as MPeM (105).

Furthermore, Hoang *et al* (106) recently established the ENLIGHT-Deep Pathology for Transcriptomics (DeepPT) approach, which is DeepPT combined with ENLIGHT DeepPT is a deep-learning framework that predicts genome-wide tumor mRNA expression levels from hematoxylin and eosin slides. The predicted genome-wide tumor mRNA expression serves as an input for ENLIGHT to generate an EMS to predict the response of a patient to therapy. Patients with lung, cervical and head and neck cancers received an ENLIGHT-matched therapy of bintrafusp alfa, a bi-specific antibody targeting TGF-β and PD-L1, and they exhibited a more favorable odds ratio of response than expected by chance (however, the data is not yet peer-reviewed). ENLIGHT-DeepPT may be a promising approach to guide immunotherapy, whilst also making transcriptome-based biomarkers more feasible in the clinical practice.

Therefore, transcriptome-based biomarkers are promising, as they seem to provide more comprehensive and valuable information. Nevertheless, the veracity of the SR-score, EMS and ENLIGHT-DeepPT require further testing in carefully controlled prospective clinical trials.

7. Conclusions and future directions

ICB-based therapy has rapidly emerged as a principal therapeutic modality for numerous solid tumors owing to its efficacy. Notably, the efficacy of ICB-based therapy depends on multiple factors, from tumor-specific neoantigen formation to neoantigen processing and presentation, then to tumor cell interactions with effector cells and the TME, among other factors. Regarding ICB-based therapy, the goal of anti-PD-1/anti-PD-L1 therapy is to reactivate cytotoxic T cells within the TME against tumor cells. Therefore, it is inevitable that the majority of tumors show primary or secondary resistance. Thus, it is critical to stratify patients with MPeM and develop novel therapeutic strategies targeting the other factors underlying the pathogenesis of MPeM.

At present, there have been several exploratory studies regarding MPeM treatment, primarily targeting the components beyond PD-1/PD-L1 within the TME, or targeting abnormal molecular and signaling pathway alterations within tumor cells. The former includes targeting mast cells to restore/promote T cell infiltration within the TME, chemokines and cytokines for the modulation of TLS neogenesis, and vascular endothelial growth factor/vascular endothelial growth factor receptor to inhibit neovascularization, among other approaches (47,107-109). The latter includes targeting the PI3K/mTOR pathway, Hippo-Yes-associated protein pathway, BAP1-/BRCA1-deficiency, anaplastic lymphoma kinase rearrangements, focal adhesion kinase phosphorylation, fibroblast growth factor receptor inhibition and histone deacetylase inhibitor inhibition, among other targets (110-116). Although these therapeutic approaches have shown antitumor efficacy to a certain degree, further studies are still required. Moreover, given the complicated alterations that can occur within tumor cells themselves and the TME, combination treatment seems to be the most promising approach (8).

The aim of the present review was to highlight predictive biomarkers to guide ICB-based therapy (Fig. 1). The aforementioned biomarkers only reflect a small portion of the tumor-associated alterations that likely occur in MPeM. Therefore, combining multiple parameters to develop predictive biomarker profiles is a more common-sense approach. This principle is also applicable to other therapeutic strategies, including combination treatment. However, this requires not only a deep understanding of the alterations of tumors themselves and the TME, but also the development of appropriate tools to analyze these alterations. In this regard, artificial intelligence-based approaches may be a valuable tool (117,118).

In conclusion, a wider range of appropriate biomarkers in MPeM pathogenesis are also required to guide ICB-based therapy and other novel therapeutic strategies.

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CW performed the review. CW, YZ and WL contributed to the writing and editing of the manuscript. All authors have read and approved the final manuscript and have full access to all the data in the study and take responsibility for the integrity and security of the data. Data authentication is not applicable.

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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