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The Evolving Therapeutic Landscape for Malignant Pleural Mesothelioma

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Abstract

Purpose of Review For patients with malignant pleural mesothelioma, prognosis is poor with extremely low 5-year survival rates and limited therapeutic options. Here, we review the current treatment landscape for mesothelioma and highlight promising future therapeutic directions.

Recent Findings Evolving frontline therapeutic options for mesothelioma include VEGF inhibition in combination with chemotherapy and dual immune checkpoint inhibition, with synergisms between the therapies and response prediction via biomarkers also being explored. Evolving experimental treatments for mesothelioma include PARP and ALK inhibitors, dendritic and CAR T-cell therapies, anti-mesothelin vaccines, and oncolytic viral therapies, representing timely advances in the field.

Summary The therapeutic landscape for malignant pleural mesothelioma is evolving and preferred treatment in the frontline and later settings will likely evolve with it. However, this does not preclude the evidence for including multi-modal therapies spanning angiogenesis and immune checkpoint inhibitors, and biomarker utilization, in current clinical trials and management.

Keywords Malignant pleural mesothelioma · VEGF inhibition · Immunotherapy · Genetic targets · CAR T-cell therapy · Mesothelioma biomarkers

Introduction

Mesothelioma is an aggressive malignancy arising from cells of the mesothelium, a serous membrane that forms the outer linings of the thoracic and abdominal cavities (hence, pleural and peritoneal mesothelioma), but also the heart and testes (hence, pericardial and testicular/tunica vaginalis mesothelioma). This article focuses on malignant pleural mesothelioma (MPM), which accounts for 80–90% of reported mesothelioma cases (followed by peritoneal mesothelioma, which accounts for the near remainder of cases and will be briefly mentioned in this article as well).

Malignant pleural mesothelioma outcomes have been dismal, with 5-year survival rates of 5–10% [1]. Prognosis can be further stratified among the histologic subtypes along the continuum of pleural mesothelioma. The most common subtype, epithelioid, represents 50–70% of cases, resembles benign, reactive mesothelial cells, and is associated with the most favorable prognosis [2]. In contrast, the sarcomatoid subtype represents 10–20% of cases, comprises of spindle cells, and is invasive, typically resistant to cytotoxic therapy, and thus associated with the worst prognosis (median survival 4 months in some studies) [1, 3]. The remaining subtype, biphasic, represents 30–40% of cases, has both epithelioid and sarcomatoid features, and accordingly carries a prognosis between the two.

Other established and emerging prognostic factors include the European Organization for Research and Treatment of Cancer (EORTC) composite score which takes into account histology with age, gender, leukocyte count, and probability of diagnosis [4], the endoplasmic reticulum stress marker CHOP [5], the stromal marker CD31 [6], the monocarboxylate transporter 4 (MCT4) [7], and the

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epithelial-mesenchymal transition related molecules periostin and phosphatase and tensin homolog (PTEN) [8]. More recent studies have shown that expression of B7 homolog 1 (B7-H1; aka programmed cell death 1 ligand 1) [9], presence of weight loss, anemia, and low albumin [10], and mesothelioma prognostic test (MPT) poor risk combined with tumor volume greater than 200 cm^3 [11] are associated with poor survival in MPM. Taking these tumor and patient factors into account allows for improved treatment stratification and prognostication compared to that of traditional clinical staging alone.

Despite insights gained from these various prognostic factors, high morbidity and mortality persist in MPM, necessitating the need for new directions in therapy. In this review, we will summarize current therapies in MPM, their strengths and weaknesses, the evolving therapeutic landscape, and its implications for current and future practice.

The Current Therapeutic Landscape

MPM can be difficult to identify early, as its early development is often asymptomatic. Instead, patients with MPM tend to present late in the disease course once dyspnea or chest pain has resulted, for example, due to tumor encasement of the lung, pleural effusion, and/or direct invasion of the tumor into the chest wall or mediastinum. These are the most common presenting symptoms, along with malaise, fatigue, anorexia, weight loss, and sweats, which often become more frequent with disease progression [12].

Due to this presentation pattern, the majority of patients with MPM do not present with early-stage disease and therefore are not amenable to local therapies such as surgery or radiation. For the minority of patients who do present with early-stage disease and have detailed preoperative staging and assessment of performance status and cardiopulmonary reserve and are ultimately deemed appropriate for surgery, current surgical options are discussed briefly below, along with radiotherapy approaches. This will be followed by a larger discussion of current systemic treatment options, keeping in mind that this is the treatment form applicable to the majority of patients with MPM.

Surgery and Radiotherapy

The spectrum of surgical approaches for MPM includes partial pleurectomy (partial removal of involved pleura), pleurectomy-decortication (removal of parietal and visceral pleura and any portions of involved lung), extended pleurectomy-decortication (removal of parietal and visceral pleura, visible tumor, pericardium, and hemidiaphragm), and extrapleural pneumonectomy (removal of the lung, pleura, pericardium, and hemidiaphragm with the goal of macroscopic complete resection (MCR)) [13, 14].

In this spectrum of surgical approaches, the most radical approach, extrapleural pneumonectomy (EPP), has 5-year survival rates of 14% with median survival of 18 months [15]. However, in the first randomized trial of EPP and postoperative radiotherapy versus no EPP/radiotherapy (both in the context of standard platinum based chemotherapy), the surgical group demonstrated shorter overall survival (OS) (14.4 versus 19.5 months) and significantly higher morbidity (surgical and radiation complications included reoperation, cardiopulmonary complications, infection, pneumonitis, ascites, pain, and death) [16]. While the results of this UK-based Mesothelioma and Radical Surgery (MARS) randomized feasibility study were negative, it has been argued that the considerable dropout rate in the originally screened group as well as the ultimate surgery and radiotherapy groups, and the more favorable biological disease in the nonsurgical group, may have problematically influenced the study outcome [17]. On the opposite end of the surgical spectrum, partial pleurectomy (PP), the least radical option, also did not result in improved survival (52% 1-year survival in PP versus 57% 1-year survival in talc pleurodesis) but saw more complications and longer hospital stays [18]. Consequently, the ongoing MARS2 study is investigating the only other radical treatment option remaining, extended pleurectomy-decortication (EPD) [19••]. It is comparing EPD versus no EPD, again in the context of a standard chemotherapy backbone, and will be the first randomized trial of its kind on a topic that has largely been contributed to by retrospective case series until now.

Radiotherapy trials have also been limited, with existing randomized data not yet showing improved survival such as in the phase II SAKK 17/04 trial where hemithoracic radiation after neoadjuvant chemotherapy and extrapleural pneumonectomy demonstrated median survival 19.3 months in the radiation group versus 20.8 months in the group without radiation, representing additional treatment burden without benefit [20]. Similarly, negative results were seen in randomized trials for prophylactic irradiation to prevent chest wall invasion after diagnostic/therapeutic procedures, as in the phase III Prophylactic Irradiation of Tracts (PIT) [21] and the phase III Surgical and Large-Bore Procedures in Malignant Pleural Mesothelioma and Radiotherapy trial (SMART trial) [22]. Ongoing randomized trials are evaluating the role of intensity-modulated radiotherapy [23] and radiotherapy in pain control [24]. If negative results are also seen in these studies, the role for routine radiotherapy will be further undermined.

Systemic Therapy

The first frontline standard of care systemic therapy regimen was defined by the phase III EMPHACIS study which showed superior median overall survival in the cisplatin with pemetrexed group (12.1 months) compared to the cisplatin alone group (9.3 months) and thus received Food and Drug Administration (FDA) approval in 2004 [25]. Similarly, cisplatin with raltitrexed was shown to be superior to cisplatin alone (11.4 versus 8.8 months median overall survival and no difference in health related quality of life measurement scales), confirming that cisplatin with an antifolate was superior to cisplatin alone in patients with MPM, without severe detriment to health related quality of life [26]. Just as single agent cisplatin fell to the background as standard of care treatment, the phase II CALGB 9530 study showed that single agent gemcitabine also had no role in MPM as its use in the frontline setting resulted in no complete or partial responses [27]. Having established the utility of frontline pemetrexed and platinum therapy, the phase II CALGB 30,901 study investigated the role of maintenance pemetrexed versus observation after frontline therapy and did not show significant increases in median progression free survival (PFS) or OS (3.4 versus 3 months, and 16.3 versus 11.8 months, respectively, both p-values > 0.6) [28], although the accrual goals for this study were not met.

In the continued search for targeted therapy, angiogenesis, a hallmark of cancer, has been targeted in mesothelioma with mixed results. Multikinase inhibitors that target multiple aspects of angiogenesis—such as cediranib (a TKI targeting VEGFR 1–3, c-Kit, and PDGFR-β) and nintedanib (a TKI targeting VEGFR 1–3, FGFR 1–3, and PDGFR α/β and Src-family members)—initially seemed effective when combined with chemotherapy in MPM, but ultimately were limited by toxicity and lack of reproducibility in larger studies, respectively [29, 30, 31, 32]. More promising results were seen in the phase III MAPS study, demonstrating that bevacizumab, a humanized anti–VEGF-A monoclonal antibody, when combined with chemotherapy in MPM in the frontline setting, improved survival compared to chemotherapy alone (median OS:18.8 months vs. 16.1 months, $p < 0.02$) [33]. These results led to bevacizumab's inclusion into the US National Comprehensive Cancer Network (NCCN) guidelines as potential first-line treatment for unresectable MPM, though it has not gained FDA approval for MPM. Similarly, the phase II RAMES study demonstrated a survival advantage when ramucirumab, a humanized anti-VEGFR2 monoclonal antibody, was combined with gemcitabine, as compared to chemotherapy alone (median OS: 13.8 months vs. 7.5 months, $p < 0.03$), in patients with previously treated MPM (patients who had experienced disease progression during or after first-line pemetrexed/platinum-based chemotherapy) [34••]. However, as of March 2022, ramucirumab with gemcitabine has not yet been included in NCCN guidelines or gained FDA approval for this indication.

A promising target that has been transformative for various solid tumors is immune checkpoint inhibition (ICI), and multiple trials are showing clinical benefit of ICI in mesothelioma as well. While the phase III PROMISE-Meso trial did not show a survival benefit for pembrolizumab (PD-1 inhibitor) over standard chemotherapy for relapsed MPM [35•], the phase III CONFIRM trial showed a survival benefit for nivolumab (PD-1 inhibitor) over placebo for relapsed MPM (overall survival 10.2 months vs. 6.9 months, $p < 0.01$) [36•]. Furthering the argument for ICI incorporation into MPM treatment, the phase III CheckMate 743 trial showed an OS benefit for nivolumab plus ipilimumab (PD-1 plus CTLA-4 inhibitor) versus chemotherapy in patients with untreated, unresectable MPM (18.1 months vs. 14.1 months, $p < 0.01$) [37••]. The survival benefit was more pronounced in patients with non-epithelioid variants of mesothelioma, often with notable responses comparable to that seen in Fig. 1. Accordingly, this first-in-class regimen is now approved by the FDA for frontline use, marking a significant stride forward in MPM treatment. CM743 did not include a VEGF inhibitor in the control arm given the timing of the initiation of that trial and the lack of regulatory approval of bevacizumab, though combined VEGF and immune checkpoint inhibition is now being explored as will be discussed below.

The Evolving Therapeutic Landscape

Chemoimmunotherapy

Building on the promising results of ICI therapy, the phase II DREAM study: Durvalumab with first-line chemotherapy in previously untreated malignant pleural mesothelioma found that durvalumab, an anti-PD-L1 antibody, given during and after platinum-pemetrexed chemotherapy, resulted in 57% of patients achieving progression free survival at 6 months and median OS 18.4 months [38•], prompting a phase III study for further investigation. Accordingly, the phase III DREAM3R study: Durvalumab with chemotherapy as first line treatment in advanced pleural mesothelioma is recruiting patients to compare frontline durvalumab with chemotherapy followed by maintenance durvalumab vs. frontline chemotherapy alone followed by observation [39••]. It will also be interesting to see if this trial confirms findings seen in the recent phase 2 PrE0505 trial, where concurrent durvalumab with platinum-based chemotherapy reached a median survival of 20.4 months versus 12.1 months with historical control [40]. The PrE0505 trial also interestingly noted that patients with germline alterations in cancer predisposing genes, especially those involved in DNA repair,

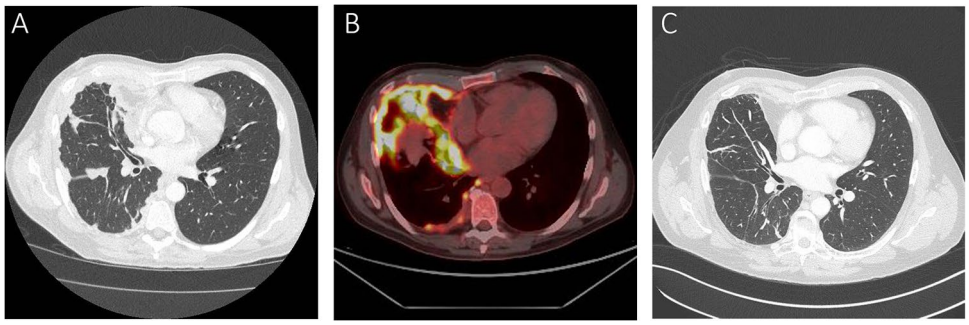

Fig. 1 Treatment response in a 61 year old male patient with malignant pleural mesothelioma, biphasic type, on dual immune checkpoint inhibitor (ICI) therapy. **A** Pre-treatment computed tomography (CT) chest at time of diagnosis shows a nodular pleural tumor in the right hemithorax. The tumor encased the lung from the apex to costophrenic angles with thickness greater than 2 cm in some areas, and nodular tumor directly invading mediastinal fat. **B** Pre-treatment positron emission tomography–computed tomography (PET-CT) following diagnosis of mesothelioma shows extensive hypermetabolic pleural-based soft tissue nodularity throughout the right hemithorax including the fissures and mediastinal fat. **C** Post-treatment CT chest, after 4 months of dual ICI therapy with nivolumab 360 mg every 3 weeks and ipilimumab 1 mg/kg every 6 weeks demonstrates that the previously extensive right sided pleural nodularity has significantly decreased and is now barely apparent. This patient's presenting symptoms of dyspnea and chest wall pain resolved and he felt well overall. Treatment was complicated by acute kidney injury that was attributed to ICI-induced nephritis and improved with oral steroids

were more likely to achieve long-term survival [40]. The Canadian Cancer Trials Group is also investigating immunotherapy with standard chemotherapy in a randomized phase II/III study of pembrolizumab (a PD-1 inhibitor) with frontline chemotherapy vs. chemotherapy alone [41••]. Positive results would help prove the synergism between ICI therapy and chemotherapy that has become standard of care for other thoracic malignancies such as small cell lung cancer [42] and non-small cell lung cancer (NSCLC) [43].

Similarly, synergisms between ICI therapy, chemotherapy, and anti-angiogenesis therapy are also being explored. While MAPS and RAMES showed benefit of anti-angiogenesis therapy in combination with chemotherapy, the BEAT-meso study is investigating whether the addition of immunotherapy to chemotherapy and bevacizumab improves outcomes compared to chemotherapy with bevacizumab alone in the frontline MPM setting. This multicenter, randomized, phase III study is estimated to reach completion in 2024 [44••].

The positive outcomes of ICI therapy in MPM are somewhat unexpected since the tumor types that have seen clear survival benefit from ICI therapy typically have high tumor mutational burden, while MPM has a very low mutation burden [45, 46]. Thus, identifying biomarkers to predict outcomes and guide the use of ICI therapy in MPM would be of significant utility. To this aim, work has been done to investigate genomic structural variants in mesothelioma. Recently, it was shown that chromosomal rearrangements are present in mesothelioma and have neo-antigenic potential [47]. A more recent study investigating tumor junction burden and antigen presentation as biomarkers in MPM treated with ICI found that tumor junction burdens were not predictive of OS but an interaction between the junction burden and "the regulation of antigen processing and presentation of peptide antigen" gene set was predictive of overall survival [48•]. The recent PrE050 trial also identified that higher degrees of genomic instability were correlated with survival outcomes [40]. These findings suggest that further work in genomic approaches to evaluate junction burdens and antigen processing and presentation may help stratify and prognosticate patients being considered for ICI therapy.

Other Immune Targets

Dendritic and CAR T-Cell Therapies

A pivotal approach in engaging the immune system to target tumor cells has been seen with genetically engineered chimeric antigen receptor T (CAR T) cell therapy, which has achieved success in hematologic malignancies [49]. Initial CAR T-cell therapies for MPM targeted the tumor-associated antigen mesothelin (a cell surface glycoprotein expressed by all epithelioid but not sarcomatoid/biphasic mesotheliomas) [50], but struggled to achieve widespread clinical response [51] and in some cases, patients suffered life threatening anaphylactic reactions [52, 53]. However, CAR T-cell function was found to be dampened by PD-1 expression, and accordingly, enhanced by PD-1 blockade with pembrolizumab [54]. Building on this mechanism, a phase I trial evaluating intrapleural CAR T-cells with pembrolizumab achieved a median overall survival of 23.9 months (1-year overall survival, 83%) [55•], suggesting a more efficacious use for CAR T-cell therapy in the future of MPM therapy.

Another developing cellular therapy in MPM involves training dendritic cells (DCs) to promote an immunostimulatory response against selected antigens. With antigen sources

spanning autologous tumor lysate [56], allogeneic tumor lysate [57], and combining dendritic cells with chemotherapy [58], clinical responses have been seen, and the currently recruiting phase II/III Dendritic Cell Immunotherapy for Mesothelioma (DENIM) trial will further clarify if there is a role for DCs in MPM [59].

Oncolytic Viral Therapies

Oncolytic viral therapies represent an appealing emerging therapy for mesothelioma as pleural/peritoneal disease involvement lends itself well to direct intratumoral injection of viral therapies. These viral therapies work through direct and indirect tumor activity, by lysing tumor cells but also by inducing immune responses. As early as 1994, human mesothelioma cell lines were found to be susceptible to adenovirus infection via a replication-deficient recombinant adenovirus carrying the *Escherichia coli* lacZ marker gene [60]. While this study showed the potential of viral vectors as vehicles for gene therapy in human mesothelioma, the ONCOS-102 study showed that ONCOS-102, a dual targeting, chimeric oncolytic adenovirus, coding for human GM-CSF, also held synergistic anti-tumor activity when combined with frontline chemotherapy [61]. Accordingly, there are now several ongoing clinical trials investigating adenoviral vectors as monotherapy [62, 63] or as multitherapy such as ONCOS-102 with carboplatin/pemetrexed [64], interferon alpha-2b with celecoxib/gemcitabine [65] or with celecoxib/pemetrexed [66], and even with ICI therapy [67]. Herpes simplex virus type 1 [68], measles virus [69], vaccinia virus [70], Newcastle disease virus [71], retrovirus [72], and reovirus [73] have also been investigated in mesothelioma, with ongoing clinical trials mostly focusing on vaccinia virus [74, 75, 76].

Genomic Targets

While MPM has a relatively low tumor mutational burden [45, 46], key tumor suppressor genes that are affected in MPM most commonly include *BAP1*, *NF2*, and *CDKN2A*. *BAP1*, or *BRCA1*-associated protein 1 carboxy-terminal hydrolase, was identified in 1998 as a nuclear protein that influenced activity of the BRCA1 protein [77], though the exact mechanism is still unclear [78, 79, 80]. It is clear, however, that individuals who inherit a *BAP1* mutant allele are at risk for developing one or more malignancies, most commonly uveal or cutaneous melanoma, clear-cell renal cell carcinoma, and mesothelioma [81, 82, 83, 84, 85]. In mesothelioma, although the mechanism is unclear, *BAP1* mutations have shown an association with better prognosis compared to sporadic disease, with as high as sevenfold improved survival [86, 87]. Due to the interaction between *BAP 1* and BRCA1, studies are now investigating for the potential to treat with PARP inhibitors, with the Mesothelioma Stratified Therapy (MiST) nonrandomized phase II trial showing that PARP inhibition with rucaparib in refractory malignant mesothelioma of any type resulted in 58% disease control at 12 weeks, 23% at 24 weeks and was well tolerated [88•]. However, a similar nonrandomized phase II trial of PARP inhibition with olaparib interestingly showed decreased PFS and OS in the germline *BAP1* mutation group compared to wild type (2.3 vs 4.1 months, and 4.6 vs 9.6 months) [89]. *BAP 1* also interacts with polycomb repressor complex 2 (PRC2) which promotes tumor growth and invasion; thus, the PRC2 inhibitor tazetostat was investigated in a phase II trial and showed 51% disease control at 12 weeks [90].

NF2 encodes Merlin, which controls the expression of oncogenic genes via a pathway involving inhibition of transcriptional co-activators YAP and TAZ, which effect the Hippo pathway [91]. Many mesothelioma specimens have aberrant YAP activation [92], and targeting this via inhibition of Rho-associated kinase (ROCK), a downstream target of YAP, or via disruption of the YAP-TEA domain transcription factor interaction using verteporfin, has been shown to impede in vitro mesothelioma cell proliferation/invasion [93, 94].

CDKN2A encodes $p16^{INK4a}$ and $p14^{ARF}$, which regulate the cell cycle by inhibiting cyclin-dependent kinase (CDK) 4 and CDK6-mediated phosphorylation of retinoblastoma protein and preventing p53 degradation, respectively [95, 96]. Many mesothelioma cases have *CDKN2A* deletion [97], and targeting this via CDK4/6 kinase inhibition with palbociclib showed synergistic ability to impede mesothelioma cell proliferation when combined with PI3K/AKT/mTOR inhibition [98]. *CDKN2A* loss has also been associated with shorter overall survival due to loss of the tumor suppressor p16ink4A, an endogenous suppressor of CDK4/6 [99]. Thus, the phase 2 MisT2 study investigated CDK4/6 inhibition with abemaciclib in p16ink4A-negative mesothelioma and found disease control at 12 weeks in 14 (54%) of 26 patients (95% *CI* 36–71) [99].

In addition to the above loss of function mutations in mesothelioma, there are also emerging case reports on oncogenic fusions, namely *EWSR1* [100, 101] and *ALK* [102, 103] in peritoneal mesothelioma, which begs the question of whether ALK-inhibition can prove successful in mesothelioma even beyond case reports, as it notably has for NSCLC [104] and other tumors [105].

Cancer Vaccines

Just as CAR T-cell therapy investigated mesothelin as a target, cancer vaccines similarly aim to stimulate the immune system to destroy mesothelioma cells by targeting mesothelin. Monoclonal antibodies targeting mesothelin have

shown acceptable tolerability and improved overall survival in phase I/II studies [106, 107], while vaccines with bacterial components (*Listeria monocytogenes* engineered to express human mesothelin [108] and *Pseudomonas* exotoxin A fused to anti-mesothelin antibody [109]) showed limited efficacy in phase I/II trials but more promising response activity when combined with chemotherapy [110, 111]. Wilms' tumor 1 (WT1) peptide analog vaccines have also shown potential response activity with immunologic adjuvants (montanide and GM-CSF) compared to adjuvants alone [112]. mRNA vaccines [113] will hopefully provide a novel platform to explore cancer immunotherapy for mesothelioma.

Cell Proliferation and Motility Targets

One regulator of cancer cell proliferation and migration is focal adhesion kinase (FAK), which is attenuated by Merlin to inhibit cancer cell migration [114, 115]. Building on this mechanism, trials of FAK inhibitors alone [116] and with MEK inhibitor trametinib [117] saw improved median PFS in Merlin-negative tumors versus Merlin-positive tumors. Another tyrosine receptor kinase important in cell proliferation and motility is MET, which is overexpressed in mesothelioma [118, 119]. Since MET inhibition via tivantinib along with PI3K inhibition suppressed tumor growth and development [120], there is now a phase I/II trial of tivantinib with frontline chemotherapy for mesothelioma and NSCLC [121].

Conclusions

Therapeutic advancements for mesothelioma have been slow due to its relative rarity and interpatient heterogeneity. However, while the incidence of malignant mesothelioma is mildly decreasing in the USA and western countries due to work practices moving away from asbestos use, its use is growing in countries such as India and China [122], pointing to the continued need for clinical research in malignant mesothelioma to improve outcomes for our current and future patients.

Thus, the therapeutic advances discussed above, spanning immune checkpoint inhibition, angiogenesis inhibition, CAR-T and dendritic cell therapies, oncolytic viral therapies, anti-mesothelin therapies, PARP, CDK 4/6, and ALK inhibition, with ongoing research into synergisms between these groups and biomarker identification to further refine and prognosticate patients among these groups, represent timely advances in the field and exciting progress in this challenging disease.

Declarations

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Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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event was thromboembolism in 4% of the ramucirumab group vs. 2% of the placebo group)..

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junctions resulting from chromosomal rearrangements and antigen processing and presentation gene set expression and estimated associations with OS using Cox models. They found that tumor junction burdens were not predictive of OS, but the "regulation of antigen processing and presentation of peptide antigen" gene set revealed an interaction with tumor junction burden and was predictive of OS. However, this interaction was not predictive of OS in a different cohort of MPM patients who did not receive immune checkpoint inhibitor (ICI) therapy. These results suggest that genomic analysis represents a tool for stratification and prognostication in MPM patients being considered for ICI therapy..

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