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Unleashing precision: A review of targeted approaches in pleural mesothelioma

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ABSTRACT

This review delves into the intricate landscape of pleural mesothelioma (PM), emphasizing the need for nuanced therapeutic strategies. While platinum-based chemotherapy remains a cornerstone, the advent of immune checkpoint inhibitors (ICIs), notably through the Checkmate 743 trial, has reshaped treatment paradigms. Challenges persist due to patient heterogeneity and a lack of specific biomarkers. Targeting genotypic and phenotypic alterations emerges as a promising avenue, demanding precision oncology in this rare disease. CDKN2A loss, prevalent in PM, may respond to CDK4/6 inhibitors. Defects in MMR and HR suggest tailored approaches with ICI or PARP inhibitors, respectively. Ongoing trials explore novel inhibitors and promising targets like mesothelin. Implementing these strategies requires overcoming challenges in patient selection, combination therapies, biomarker identification, and cost considerations. Collaboration is crucial for transforming these insights into impactful clinical interventions, heralding the era of personalized and precision medicine for PM.

1. Introduction

Pleural mesothelioma (PM), a rare and aggressive malignancy predominantly afflicting the pleura, presents a formidable challenge in oncology. This disease is strongly linked to asbestos exposure and is characterized by a notoriously poor prognosis, with a median overall survival ranging from 12 to 18 months (Robinson and Lake, 2005; Cao et al., 2014). Histologically classified into epithelioid, biphasic, and sarcomatoid subtypes, PM displays substantial heterogeneity within these categories, a factor not fully captured by the current classification (Husain et al., 2018). Mounting evidence highlights the significant role of molecular and genetic differences, heterogeneity in the tumor immune microenvironment (TIME), and dysregulation of gene expression and epigenetic changes in contributing to variable clinical outcomes (Bueno et al., 2016; Mangiante et al., 2023). Despite advances in diagnosis and treatment, therapeutic options for PM remain limited. Platinum-based chemotherapy has stood as the mainstay for over a decade (Vogelzang et al., 2003). The emergence of immune checkpoint inhibitors (ICIs) has rekindled enthusiasm for immunotherapy (IO) in PM, although initial trials using single-agent ICIs yielded conflicting results, attributed in part to the lack of specific biomarkers and the intricate intra- and inter-patient heterogeneity (Okada et al., 2019; Scherpereel et al., 2019). The landmark phase III Checkmate 743 trial has reshaped the treatment landscape by demonstrating the superiority

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of an ICI combination (nivolumab plus ipilimumab) over chemotherapy, particularly in non-epithelioid tumors. This pivotal study has established a new standard of care in the first-line setting, marking a significant milestone in PM therapeutics (Baas et al., 2021). High-throughput genomic techniques enabled precision medicine approaches in tumors, nevertheless, PM presents a complex challenge in oncology due to its molecular heterogeneity, a key aspect illuminated by recent studies. Hmeljak et al. conducted an integrative molecular characterization, revealing the intricate landscape of PM tumors, emphasizing the need for targeted therapeutic strategies (Hmeljak et al., 2018). This molecular diversity, underscored by the multi-factorial nature of heterogeneity as outlined by Mangiante et al. and their comprehensive analysis of intertumor heterogeneity, has posed a significant obstacle to the development of effective targeted therapies (Mangiante et al., 2023) The genomic landscape of PM, explored by Hiltbrunner et al., further enriches our understanding, providing insights into the distinct profiles of pleural and peritoneal mesothelioma tumors (Sekido, 2010). Despite these advancements, the translation of this molecular knowledge into targeted therapeutic interventions remains a complex task. Challenges are amplified by the intricate interplay of signaling pathways and molecular aberrations, necessitating an in-depth exploration and contextualization of preclinical and clinical studies in the PM landscape. In this comprehensive review, we aim to highlights alterations in the main signaling pathways genes, epigenetic modifications, and potential new targets for a precision oncology approach in PM.

2. Targeting RTK/RAS/MAP-Kinase pathway

Mutations in receptor tyrosine kinases-rat sarcoma-mitogen activated protein kinase (*RTK/RAS/MAPK*) genes are rare, but downstream cascades, including MAPK, are activated in most cases of PM (Sekido, 2010).

CDKN2A gene, which encodes proteins that regulate the cell cycle, is often deleted in PM, occurring in about 70 % of cases, and associated with a poor prognosis (Perera and Mansfield, 2022; Hiltbrunner et al., 2022). CDK4/6 inhibitors have shown promising results in mesothelioma models, and in particular abemaciclib, a selective CDK4/6 inhibitor, has shown clinical activity in patients with p16INK4A-negative PM (Aliagas et al., 2021; Fennell et al., 2022). Recent studies suggest that CDK4/6 inhibitors have potential in combination with chemotherapy in PM cell lines and may overcome resistance to ICIs in animal models with *CDKN2A* loss (Terenziani et al., 2022; Jang et al., 2022).

Anaplastic lymphoma kinase (*ALK*) rearrangements have been identified in up to 3 % of peritoneal mesothelioma patients and 0.36 % of PM subjects. ALK overexpression has been identified in 19.5 % of PM cases (Hiltbrunner et al., 2022). The combination of the ALK inhibitor crizotinib with the mTOR inhibitor rapamycin has shown efficacy in ALK overexpressing PM (Mönch et al., 2018). Due to the rarity of *ALK* rearrangements in PM, newer generations of ALK inhibitors have been tested just in case reports with small efficacy. A Chinese group reported a case of *EML4-ALK* PM treated with alectinib with a progression free survival (PFS) of 4.5 months and lorlatinib with a PFS of 3.5 months and overall survival (OS) of 11.7 months (Hu et al., 2020).

Epidermal growth factor receptor (*EGFR*) amplification occurs in 44–97 % of PM patients and is implicated in tumor growth and progression, but a high EGFR expression does not correlate with EGFR tyrosine kinase inhibitor sensitivity. On the contrary, *EGFR* mutations are rare in PM, with a reported prevalence of 0.3 % (Hiltbrunner et al., 2022; Chia et al., 2019). Treatment with EGFR inhibitor afatinib has been reported in a case of PM harboring rare *EGFR* mutations treated with afatinib, which achieve a partial response with a PFS of 65 days (Agatsuma et al., 2017). Novel anti-EGFR antibody drug conjugates (ADCs), such as depatuxizumab mafodotin (ABT-414), have demonstrated efficacy in PM in vivo (Chia et al., 2019).

KRAS mutations have a variable prevalence in PM, ranging from 1 % to 9 %, and miR-206 has been tested as a possible novel approach for targeting the RTK/RAS/MAPK-PI3K/Akt-CDK pathway, including direct activity against KRAS (Sanchez-Vega et al., 2018; Singh et al., 2021).

C-Met is overexpressed in 74–100 % of PM cases, but its prognostic impact remains unclear. *MET* amplification is a rare event in PM and the predictive value of *MET* alterations in PM for possible target therapy is still under evaluation (Santoni-Rugiu et al., 2021; Bois et al., 2016).

3. Targeting Hedgehog pathway

The Hedgehog signaling pathway (HP) is critical for embryonic mesothelium development and it is typically inactive in most adult tissues, including mesothelium, except for specific populations of progenitor cells (Dixit et al., 2013). Despite this, HP has been shown to be re-activated in a subgroup of PM patients with poor clinical outcomes, consistent with the restoration of developmental pathways in cancer (Shi et al., 2012). Patched 1 (PTCH1) is a transmembrane receptor that is located on the primary cilium and inhibits the activation of the G protein-coupled receptor smoothened (SMO). HP is activated when Hedgehog ligands (Sonic Hedgehog (Shh), Desert Hedgehog (Dhh), Indian Hedgehog (Ihh)) bind to PTCH1, which removes its inhibition on SMO. SMO activation causes nuclear translocation of the glioma-associated protein (GLI) family, inducing the expression of Hedgehog target genes such as *GLI1* and Hedgehog interacting protein (*HHIP*). The latter competes with PTCH1 by binding to Hedgehog ligands. The principal negative regulator of GLI-protein levels and activities is suppressor of fused (SUFU). Loss of SUFU in mammals results in global HP activation and early embryonic lethality (Corbit et al., 2005). In PM, HP upregulation may result from ligand-dependent activation (paracrine or autocrine) during mesothelium repair after tissue damage (Felley-Bosco et al., 2015). According to data from The Cancer Genome Atlas (TCGA), the HP is among the top ten most deregulated pathways in PM, and the Hedgehog target gene-expressing group was one of the two groups with the worst prognosis among the four subgroups of PM patients clustered according to mRNA expression profile (Felley-Bosco et al., 2015). High *SMO* and *Shh* expression levels have been associated with worse survival in PM patients, as well as high *GLI1* gene expression (Shi et al., 2012; Zhang et al., 2013; Signorelli et al., 2020). Comprehensive genomic profiling of tumor samples from a cohort of 1113 PM patients has revealed alterations in HP genes, specifically *PTCH1* (1.2 %) and *SUFU* (0.8 %) (Hiltbrunner et al., 2022). In vitro models have shown that SMO antagonists (such as SMO inhibitor GDC-0449 or the antifungal drug itraconazole) and GLI-inhibitors (such as GANT61 or the anti-leukemia drug arsenic trioxide) reduce PM cell viability. Treatment with the SMO antagonist vismodegib in a rat model of mesothelioma reduced the expression of target genes such as *GLI1, HHIP,* and *PTCH1*, and caused a significant reduction in tumor volume and tumor growth (You et al., 2014; Meerang et al., 2016). Clinical trials of these drugs are ongoing, but the absence of genotyping-based selection may affect outcomes. For instance, two phase I trials of vismodegib and sonidegib for the treatment of solid tumors, which included a total of 5 PM cases without any molecular selection, failed to show any clinical benefit for SMO-inhibition in PM patients (Table 1) (LoRusso et al., 2011; Rodon et al., 2014). However, Hedgehog-activating variants (Hmeljak et al., 2018), (Bueno et al., 2016; Gao et al., 2013; Cerami et al., 2012) may predict response to SMO-antagonists. For example, a durable response to vismodegib has been reported in a PM patient harboring a *PTCH1* F1147fs mutation (Popat et al., 2021). So far, no *SMO* pathogenic variants with clinical actionability have been described (Patel et al., 2020).

4. Targeting Hippo pathway

The Hippo pathway is a crucial regulator of the normal tissues' proliferation, apoptosis, polarity, and homeostasis of stem/differentiated cells. It was primarily studied in Drosophila species, and the proteins involved in this pathway can be grouped into two categories: tumor

Table 1
Target therapies in clinical trials.

Target	Drug investigated	Mechanism of action	Study/Phase	N pts	Results	Safety profile	Ref.
	RTK/RAS/MAP-Kinase Pathway						
p16ink4A-deficient	Abemaciclib	CDK4/6 inhibitor	II	26	DCR 54 %	Tox ≥ 3 AEs: 31 % (G5 4 %, neutropenic sepsis)	Fennell et al. (2022)
EML4-ALK translocation	AlectinibLorlatinib	ALK inhibitor	Case Report	1	PFS 4.5 moPFS 3.5 moOS 11.7 mo	NA	Hu et al. (2020)
EGFR mutation (G719C and S768I)	Afatinib	EGFR inhibitor	Case Report	1	PFS 2 mo	NA	Agatsuma N, (2017)
	Hedgehog Pathway						
*	Vismodegib	SMO inhibitor	I	3	ORR 0 %	Tox ≥ 3 AEs: 42,2 %hyponatremia, fatigue, abdominal pain	Lo Russo PM (2011)
*	Sonidegib	SMO inhibitor	I	2	ORR 0 %	Tox ≥ 3 AEs: < 5 %serum creatinekinase elevation,weight loss, myalgia, hyperbilirubinemia, dizzines, asthenia	Rodon J (2014)
PTCH1 mutation	Vismodegib	SMO inhibitor	Case Report	1	ORR 100 %	Tox ≥ G3 AEs: Alopecia,	Popat S (2021)
	Hippo Pathway						
Merlin/NF2 loss	Defactinib vs placebo (maintenance after I line)	FAK inhibitor	II	173/171	PFS 4.1 vs 4.0 moOS 12.7 vs 13.6 mo	Tox ≥ 3 AEs: 22,5 %heart failure, syncope,pneumonia, QT prolongation, chest pain, renal failure	Fennell DA (2019)
Merlin/NF2 loss	Everolimus	mTOR inhibitor	II	7	SD 66.7 %, PD 33.3 %	SAE 42,86 %(bleeding,constipation, neutropenia,pneumonitis)	NCT01024946 (Anon, n.d.)
*	Defactinib + VS−5584	FAK inhibitor + mTOR inhibitor	I	21	Terminated	NA	NCT02372227 (Anon, n.d.)
*	Defactinib + pembrolizumab	FAK inhibitor + anti-PD−1	IA-IB	-	Withdrawn	NA	NCT04201145 (Anon, n.d.)
Merlin/NF2 loss	GSK2256098	FAK inhibitor	I	62 (29 MM, 14 NF2 loss)	PFS 23.4 vs 11.4 vs 10.9 ws (in NF2 loss vs positive vs unknown)	Tox ≥ G3 AEs: Hypertriglyceridemia 5 % Hypokalemia 5 %CPK increase 2,5 %Cerebrovascular event 2,5 %	Soria J et al. (2016)
Merlin/NF2 loss	GSK2256098 + trametinib	FAK + MEK inhibitor	Ib	34 (14 NF2 loss)	SD 38 %, PD 62 %PFS 15 vs 7.3 w (in NF2 loss vs positive)	Tox ≥ G3 AEs: 59 %nausea, diarrhoea, decreased appetite, pruritus, fatigue, rash	Mak G et al. (2019)
*	APG−2449	FAK inhibitor	I	150	Recruiting	NA	NCT03917043 (Anon, n.d.)
Merlin/NF2 loss	Pevonedistat +/- cisplatin and pemetrexed	Neddylation/SCF complex inhibitor	I-II	9	Active, not recruiting	NA	NCT03319537 (Anon, n.d.)
YAP/TAZ fusions or NF2/LATS1/ LATS2 mutation	IAG933	Prevent YAP-TEAD interaction	I	159	Recruiting	NA	NCT04857372 (Anon, 2022)
NF2 mutations	VT3989	TEAD inhibitor	I	67	42 (29 PM, 13 non-pleural):PR+SD>8 ws: 57 %	Tox ≥ G3 AEs: fatigue, ALT/AST increase, dehydration, dyspnea, hypotension, peripheral edema cardiomyopathy	Yap TA, 2023 (Anon, n.d.)
YAP/TAZ fusions or NF2 mutation	IK−930	TEAD inhibitor	I	158	Recruiting	NA	NCT05228015 (Anon, n.d.)
	DNA damage and repair pathway						
BAP1 or BRCA2 deficient	Rucaparib	PARP inhibitor	IIa	26 (25 pleural and 1 peritoneal) (10 pts (38 %) both BAP1 and BRCA1 deficient)	DCR 58 % (12 w)DCR 23 % (24 w)PFS 17.9 wOS 41.14 w	Tox ≥ G3 AEs: Upper respiratory tract infection 12 %Anemia 12 %	Fennell DA et al. (2021)

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Table 1 (*continued*)

Target	Drug investigated	Mechanism of action	Study/Phase	N pts	Results	Safety profile	Ref.
DDR pathway gene mutation	Niraparib	PARP inhibitor	II	37	18 pts evaluable in Cohort A (tumors likely to harbor mBAP1):PR 6 % (1 pts) SD 44 % (8 pts)PD 50 % (9 pts)	Tox ≥ G3 AEs: Anemia 16 % Thrombocytopenia 16 %Nausea 11 %Vomiting 8 %	George TJ et al. (2022)
HR gene mutations	Niraparib + dostarlimab	PARP inhibitor + PD−1 inhibitor	II	12	12 pts with PM histology:mPFS 2.9 mo (2.7-NA)	Tox ≥ G3 AEs: 23 % LymphopeniaAnemia HyponatremiaHypokalemia	Passiglia F et al. (2023)
BAP1 or BRCA1 deficient	Rucaparib	PARP inhibitor	II	-	Recruiting	NA	NCT03654833 (Anon, n.d.)
	PI3K/AKT/mTOR pathway						
*	Everolimus	mTOR Inhibitor	II	59	ORR 2 %PF2 2.8 moOS 6.3 mo	Tox ≥ G3 AEs:Fatigue 10.2 %, Anemia 6.8 %, Lung infection 6.8 %	Ou SHI et al. (2015)
*	LY3023414	Dual PI3K/mTOR inhibitor	I	52	ORR 2.4 %DCR 43 %	Tox ≥ G3 AEs: 21 % Fatigue 10 %	Zauderer MG et al. (2021)
	AXL pathway						
*	Bemcentinib +pembrolizumab	AXL Inhibitor + anti-PD−1	IIa	25	Recruiting	NA	Krebs M et al. (2018)
	VEGF axis						
*	Thalidomide (maintenance) vs BSC	inhibit the production of interleukin (IL)−6	III (NVALT 5)	222 (111 in experimental arm)	mPFS 3.6 vs 3.5 mo (HR 0.95)	Tox ≥ G3 AEs: 39 % Neurosensory events, Cardiac eventsThromboembolic events)	Buikhuisen WA et al. (2013)
*	Bevacizumab + gemcitabine/ cisplatinvs Placebo + gemcitabine/cisplatin	VEGF inhibitor	II#	115	mPFS 6.9 vs 6 momOS 15.6.6 vs 14.7 mo	GCB increase any grade of:alopecia, epistaxis, hypertension, infection without neutropenia, proteinuria, stomatitis	Kindler HL et al. (2012)
*	Bevacizumab + pemetrexed/ cisplatin vs pemetrexed/cisplatin	VEGF inhibitor	III (MAPS)#	448 (223 in experimental arm)	mOS 18.8 vs 16.1 mo (HR 0.77)mPFS 9.2 vs. 7.3 mo (HR 0.61)	Tox ≥ G3 AEs: Hypertension 23 % vs 0 %Thrombotic events 6 % vs 1 %	Zalcman G et al. (2016)
*	Nintedanib + pemetrexed/ cisplatin vs Placebo+ pemetrexed/ cisplatin	VEGFR inhibitor	II (LUME –Meso)	87 (44 in experimental arm)	mPFS 9.4 vs 5.7 (HR 0.54)mOS 18.3 vs 14.2 (HR 0.77)	Tox ≥ G3 AEs: 79.5 % vs 53.7 % Neutropenia 43.2 % *vs* 12.2 %	Grosso F et al. (2017)
*	Nintedanib + pemetrexed/ cisplatin vs Placebo + pemetrexed/cisplatin	VEGF receptors 1–3, PDGF receptors α and β, FGF receptors 1–3, and Src and Abl kinases inhibitor	III (LUME –Meso) #	458 (229 in experimental arm)	mPFS 6.8 vs 7 (HR 1.01)	Tox ≥ G3 AEs:Neutropenia 32 % *vs* 24 %SAE 44 % vs 39 %:Pulmonary embolism 6 % *vs* 3 %	Scagliotti GV et al. (2019)
*	Cediranib + pemetrexed/cisplatin vs Placebo + pemetrexed/cisplatin	VEGF inhibitor	II (SWOG S0905) #	92 (45 in experimental arm)	mPFS 7.2 vs 5.6 mo (HR 0.71)mOS 10 vs 8.5 mo (HR 0.88)ORR 26 %	Tox ≥ G3 AEs: 69 % vs 57 % Hypertension 20 % vs 0 %Weight loss 9 % vs 0 %	Tsao AS et al. (2019)
*	Bevacizumab + pemetrexed/ CBDCAvsBevacizumab + Atezolizumab + pemetrexed/ CBDCA	VEGFR inhibitor + anti PD-L1	III (BEAT – Meso)	401	mPFS 9.2 vs 7.6 mo (HR 0.75)mOS 20.5 vs 18.1 mo (HR: ITT 0.84, non-epitelioid 0.51, epitelioid 1.01)ORR 55 % vs 49 %	Tox ≥ G3 Aes: 55 % vs 47 %G5: 7 pts vs 1 pt,	Popat S et al. (2024)
*	Sunitinib	VEGFR, PDGFR and KIT inhibitor	II	53	ORR 12 %	Tox ≥ G3 AEs:Thrombocytopenia 9 %Neutropenia 7 %	Nowak AK et al. (2012)
*	Vatalanib		II (CALGB 30107)	47	mPFS 4.1 mo3mo PFS 55 %	Tox ≥ G3 AEs:neutropenia 2 % nausea 15 %ALT elevations 11 % AST elevation 6 %	Jahan T et al. (2012)
	Nintedanib + pembrolizuf[mab	VEGFR inhibitor + PD−1 inhibitor	Ib	30	mPFR 6,2 momOS 14,1 moORR 24,1 % (PR 7/ 29)SD 58,6 % (17/29)PD 17,2 % (5/29)	Tox ≥ G3 AEs:Lipase increased 10 % Myocarditis 7 %Colitis 3 %Skin disorders 7 %Dyspnea 7 %	Danlos FX et al. (2023)
	Pembrolizumab + lenvatinib	PD−1 inhibitor + antiangiogenic multikinase inhibitor	II	38	ORR 45 % (17/38)	Tox ≥ G3 AEs:Hypertension 21 % Anorexia 11 %Lymphopenia 11 %	Douma L et al. (2023)

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Table 1 (*continued*)

Target	Drug investigated	Mechanism of action	Study/Phase	N pts	Results	Safety profile	Ref.
						SAE 26 % (1 death for myocardial infarction)	
*	Ramucirumab + gemcitabine vs Placebo + gemcitabine	VEGFR−2 inhibitor	II (RAMES)#	161	mOS 13.8 vs 7.5mo (HR 0.71)	Tox ≥ G3 AEs:Neutropenia 20 % vs 12 % Hypertension 6 % vs 0 %SAEs: 6 % vs 5 %	Pinto C et al. (2021)
	Epigenetics						
*	Dihydro−5-azacytidine	DNA methylation inhibitor	II	41	ORR 17 %	Tox ≥ G3 AEs:Anemia 15 % Arrythmia 19 %Pericardial effusion 16 %	Vogelzang NJ et al. (1997)
BAP1 loss	Tazemetostat	Histone methyltransferase inhibitor	II	61	DCR was 54 %mPFS 18 w	Tox ≥ G3 AEs 16 %:Hyperglycaemia 7 % Hyponatraemia 7 %SAEs: 34 %	Zauderer MG et al. (2022)
*	Vorinostat	Histone deacetylase inhibitor	I	13	2 PR4 SD	NA	Kelly WK et al. (2005)
*	Vorinostat vs Placebo	Histone deacetylase inhibitor	III (VANTAGE−014)	661 (329 in experimental arm)	mOS 30.7 vs 27.1 w (HR 0.98)mPFS 6.3 vs 6.1 w (HR 0.75)	Tox ≥ G3 AEs:Anemia 5 % vs 1 % Nausea 7 % vs 1 %	Krug LM et al. (2015)
	Mesothelin						
*	SS1P	Recombinant Anti-Mesothelin Immunotoxin	I	7	2 PR	Tox ≥ G3 AEs:Hypoxia 12 %	Hassan R et al. (2007)
*	SS1P + pemetrexed/platinum	Recombinant Anti-Mesothelin Immunotoxin	I	24	12 PR3 SD5 PD	Tox ≥ G3 AEs:Hypoalbuminemia 21 %Hypotension 8 %	Hassan R et al. (Hassan et al., 2014)
*	SS1P + pentostatin + cyclophosphamide	Recombinant Anti-Mesothelin Immunotoxin	I/II	9	1 PR3 SD4 PD	SAEs: Respiratory failure, Atrial fibrillation, Acute kidney injury	NCT01362790 (Anon, n.d.)
*	LMB−100 + ipilimumab	Humanized anti-MSLN Fab fragment	I	20	Recruiting	NA	NCT04840615 (Anon, n.d.)
*	Anetumab ravtansine	antibody–drug conjugate anti-MSLN conjugated to the maytansine derivative tubulin inhibitor DM4	I	35	4 PR19 SD11 PD	Tox ≥ G3 AEs 29 %Nausea 8 % Keratitis 5 %SAEs: 13 %	Hassan R et al. (2020)
Mesothelin 2+ or 3+ IHC	Anetumab ravtansine vsvinorelbine	antibody–drug conjugate anti-MSLN conjugated to the maytansine derivative tubulin inhibitor DM4	II	166	mPFS 4.3mo vs 4.5 (HR 1.22)ORR 9.6 % vs 7.3 % DCR 73.5 % vs 56 %	Tox ≥ G3 AEs:Anemia 1 % vs 39 % Neutropenia 1 % vs 17 %Corneal disorder 2 % vs 0 %	Kindler HL et al. (2022)
Mesothelin 2+ or 3+ IHC	Gavocabtagene autoleucel (gavo-cel; TC−210) +/- immuno-oncology agents	autologous genetically engineered T cells expressing a single-domain antibody that recognizes human Mesothelin, fused to the CD3-epsilon subunit which, upon expression, is incorporated into the endogenous T cell receptor (TCR) complex.	I/II	175	Recruiting mPFS 177 dmOS 337 d	Tox ≥ G3 AEs:Cytokine Release Syndrom 25 %	NCT03907852 (Anon, n.d.)
Mesothelin 2+ or 3+ IHC	TC−510	autologous genetically engineered T cells expressing: a single-domain antibody that recognizes Mesothelin and CD3-epsilon subunit incorporated into the endogenous T cell receptor (TCR) complex and second, a PD−1: CD28 switch receptor expressed on the surface of the T cell, independently from the TCR.	I/II	115	Recruiting	NA	NCT05451849 (Anon, n.d.)
Mesothelin expression	Lentiviral transduced huCART-meso cells with or without lymphodepletion	CAR-T targeting mesothelin	I	27	Recruiting	NA	NCT03054298 (Anon, n.d)
Mesothelin 2+ or 3+ IHC	autologous mesothelin (MSLN)-targeted chimeric antigen receptor (MSLN-CAR) T cells secreting PD−1 nanobodies (αPD1-MSLN-CAR T cells)	CAR-T targeting mesothelin	I	10	Recruiting	NA	NCT04489862 (Anon, n.d.)

*No alteration selection. #Phase II and III positive trial resulted for primary endpoints. DCR: disease control rate; ORR: overall response rate; PFS: progression free survival; OS: overall survival; SD: stable disease, PD: progressive disease; Months: mo. BSC: best supportive care. HR: hazard ratio; w: weeks; IHC: immunohistochemistry; d: days

suppressors and pro-oncogene regulators. The activation of upstream oncosuppressors leads to the phosphorylation of YAP-TAZ, preventing the expression of nuclear genes responsible for cell growth (Ma et al., 2019). Conversely, inactivation of oncosuppressors, such as during development or acquired alterations, allows YAP-TAZ to exert its tumorigenic functions by translocating into the nucleus (Rausch and Hansen, 2020; Boggiano and Fehon, 2012). In solid tumors, an increased concentration of YAP-TAZ in the nucleus is linked to poor prognosis (Janse van Rensburg and Yang, 2016; Shreberk-Shaked and Oren, 2019). In PM, 70 % of tumors shows deregulation of Hippo pathway, leading to the activation of YAP (Murakami et al., 2011).

The most frequent gene alteration in Hippo is the loss of function of neurofibromatosis 2 (*NF2*) (Bueno et al., 2016; Lo Iacono et al., 2015). *NF2* activity contributes to the maintenance of cell polarity and inhibition of proliferation and invasion through the production of merlin, which is a negative growth control factor (Morrison et al., 2001; Sekido, 2013). High levels of hyaluronic acid (HA) or *NF2*-loss have shown to be able to promote tumor progression and drug resistance by modulating the expression of genes that increase cell invasion and expulsion of anti-cancer treatments (Senbanjo and Chellaiah, 2017; Orian-Rousseau, 2015). The inhibition of CD44 through lipid nanoparticles composed of HA analog conjugated with cisplatin can prevent pro-tumorigenic functions and results in the suppression of PM growth in vitro (Ohno et al., 2018; Fujimoto et al., 2013; Sakurai et al., 2019). Due to increased dependence on FAK signaling in *NF2*-loss PM, FAK inhibitors, such as VS-4718, have demonstrated promising anti-tumoral properties in vitro in *NF2*-deficient PM (Shapiro et al., 2014). However, their use as maintenance monotherapy has failed to show clinical benefit in a phase II trial (Fennell et al., 2019). Another FAK inhibitor, GSK2256098, has shown enhanced clinical benefit in solid tumors, particularly in *NF2*-loss PM, both alone and in combination with a MEK inhibitor (Soria et al., 2016; Mak et al., 2019). In combination with other strategies, FAK inhibitors have also been tested in *NF2*-deficient tumors, with limited results (Anon, n.d.; Anon, n.d.; Anon, n.d.). In *NF2*-loss cells, Cullin-4 (CUL4), stimulated by the binding with neural precursor cell expressed developmentally downregulated 8 (NEDD8), a process call neddylation, can deregulate cell growth and promote tumor progression. Pevonedistat, a neddylation inhibitor, has shown promising *in vitro* results and is being tested in a phase I-II trial with cisplatin and pemetrexed (Meerang et al., 2020; Salaroglio et al., 2022; Anon, n.d.).

Silencing of the upstream oncosuppressor Ras Association Domain-Containing Protein 1 (*RASSF1A*) accounts for 20 % of PM alterations and is associated with poor prognosis (Fischer et al., 2006; Destro et al., 2008). Demethylating *RASSF1A* promoter by DNA methyl-transferase inhibitors can increase the activation of the Hippo pathway, resulting in the reduction of tumor growth in rhabdomyosarcoma cells (Slemmons et al., 2020).

Other common alterations of Hippo pathway found in PM core kinases are the methylation of Macrophage Stimulating 1 (*MST1*) promoter and homozygous deletion/point mutation of *LATS2*, both leading to increased concentration of YAP in the nucleus (Murakami et al., 2011; Maille et al., 2019; Tranchant et al., 2017). A potential approach to restore Hippo function involves increasing the activity of upstream kinases to induce YAP-TAZ (Maille et al., 2019; Johnson and Halder, 2013). Another strategy to prevent YAP function is to prevent its binding to the transcriptional enhancer factor domain (TEAD) family, which results in transcriptional blocking (Liu-Chittenden et al., 2012; Kaneda et al., 2020). Several molecules targeting TEAD are under evaluation in phase I clinical trials, and first preliminary results seems encouraging (Anon, n.d.; Anon, n.d.).

5. Targeting DNA damage and repair pathway

The DNA Damage Response (DDR) pathway coordinates the identification, signaling, and repair of DNA damage caused by endogenous or exogenous factors, preventing cancerous cell formation (Jackson and Bartek, 2009). DNA repair during the cell cycle minimizes the chance of passing DNA damage permanently during cell division (Jackson and Bartek, 2009). Unrepaired severe DNA damage may stop apoptosis and favor cancer cell proliferation. The DDR consists of 5 distinct pathways: base excision repair (BER), nucleotide excision repair (NER), homologous recombination (HR), mismatch repair (MMR), and non-homologous end joining (NHEJ) (Gavande et al., 2016). A Study reported up to 46 % germ line or acquired mutations in DDR genes, with exclusively 40 % in the HR pathway in PM patients (Panou et al., 2018).

Expression of the DNA damage and repair pathway has shown to influence the prognosis of PM patients. It was downregulated in patients with very long survival, associated with a lower percentage of double positive RAD51/BRCA1 cells, suggesting an increased sensitivity of these tumors to standard chemotherapy (Ganzinelli et al., 2023).

A study identified an association between PM patients and polymorphisms in X-Ray Repair Cross Complementing 1 (*XRCC1*) and Excision Repair 1 (*ERCC1*) repair genes, strengthening the hypothesis of a role for genetic risk factors in asbestos carcinogenicity (Betti et al., 2011). The poly [ADP-ribose] polymerase 1 (PARP1), a DNA damage sensor, has been attempted to repair DNA in other pathways like HR and NHEJ but not directly targeting XRCC1 or ERCC1 alterations in PM (Toumpanakis and Theocharis, 2011; Ray Chaudhuri and Nussenzweig, 2017).

According to literature data, *BRCA2* alterations can be found in 2–8 % and *BAP1* mutations in about 45 % of cases of PM (Hiltbrunner et al., 2022; Panou et al., 2018). Tumors with defects in HR may be susceptible to PARP inhibition, including tumors with BRCA1-associated protein (*BAP1*)-deficiency (Parrotta et al., 2017). The PARP inhibitor, rucaparib, has shown some activity in PM patients with *BAP1* and *BRCA2* alterations in a recent Phase IIa clinical trial (Fennell et al., 2021). A Phase II testing the effect of niraparib on patients with neoplasm likely to harbor *BAP1* mutation failed to meet the pre-specified ORR threshold for efficacy but showed a clinical benefit in 78 % of patients whose *BAP1* mutations was confirmed on tissue (George et al., 2022). However, a recent study assessing the efficacy of combining PARP inhibitor niraparib with PD-1 Inhibitor dostarlimab has shown potential benefit of this combo in PM patients harboring *BRCA2* p.A406Lfs*9 variant (Passiglia et al., 2023). Trabectedin and ICI are other anticancer agents that may have a role in PM with alterations in the DDR pathway. In vitro studies have shown a positive correlation between HR deficiency and response to trabectedin for the treatment of different types of neoplasms (Tavecchio et al., 2008).

The MMR system recognizes and repairs erroneous insertion, deletion, and mis-incorporation of bases, which can arise during DNA replication and recombination, as well as repairing some forms of DNA damage (Larrea et al., 2010). Inactivation of the MMR genes causes microsatellite instability (MSI) which is a predictive biomarker of response to ICI, although no studies on ICI in MSI PM have been conducted yet (Losi et al., 2019; Arulananda et al., 2018).

6. Targeting PI3K/AKT/mTOR pathway

The Phosphoinositide 3-kinase/Protein kinase B/mammalian target of rapamicin (PI3K/AKT/mTOR) pathway controls the cell cycle, including cellular quiescence, proliferation, and tumorigenesis, and is upregulated in many cancer types, including PM. Although the exact mechanisms of hyperactivation of this pathway in PM are not completely understood, downregulation of Inositol Polyphosphate-4-Phosphatase Type I A (INPP4A), one of the phosphatases affecting the PI3K/AKT/mTOR pathway, has been observed in 44 % of PM cases, while overexpression of PI3K components has been associated with activating mutations in 9 % of cases (Guo et al., 2015; Chaudhuri et al., 2018). Additionally, hyperactivation of the PI3K pathway may be a mechanism of progression or resistance to standard chemotherapy in PM.

Bitanihirwe et al. demonstrated that the expression of phospho-

mTOR influenced the prognosis of patients with resectable PM receiving multimodal therapy, suggesting the potential role for mTOR-targeted treatments during multimodal therapy for PM (Bitanihirwe et al., 2014). Although the primary endpoint of the phase II trial SWOG S0722, testing the selective mTOR inhibitor everolimus in pre-treated advanced PM, was not reached, preclinical studies have been conducted to test novel combination therapies to overcome anti-tumor resistance to mTOR targeting agents (Ou et al., 2015). For instance, the addition of multi-targeted agents to everolimus resulted in synergistic activity in vitro (Pignochino et al., 2015). Two different PI3K/AKT/mTOR inhibitors, NVP-BEZ235 and GDC-0980, were also tested in PM cell lines, with both inducing long-term autophagy but not cell death. However, the addition of chloroquine, an inhibitor of autophagy, was able to overcome drug resistance and determined cell death through caspase-dependent phenomena (Echeverry et al., 2015). Moreover, the sequential combination of palbociclib, a CDK4 inhibitor, plus BEZ235 and BYL719 (PI3K/AKT/mTOR inhibitors), caused the overexpression of p53 and p21, leading to PM cell proliferation inhibition through sustained cellular senescence (Bonelli et al., 2017).

Among various ATP-competitive AKT inhibitors, afuresertib has emerged as the one with higher anti-tumor effects in PM cells through activation of apoptosis cascade by caspase 3 and caspase 7. However, the use of this drug is limited by the evidence of overlapping cytotoxicity with cisplatin (Yamaji et al., 2017). Recently, the selective ATP-competitive inhibitor of class I PI3K isoforms, mTORC1/2, and DNA-PK, LY3023414, has passed phase I trial evaluation and has been tested in a cohort of forty-two patients with advanced PM, resistant to prior therapy, or ineligible for standard of care (Zauderer et al., 2021).

Currently, the therapeutic strategy with the highest potential to move on in clinical trials evaluation is represented by the combination of MEK and p110b/PI3K pathway inhibitors, selumetinib, and AZD8186. The combination of selumetinib and AZD8186 in preclinical PM models displayed high anti-tumor efficacy, especially in sarcomatoid histology, mediated by activation of Phosphatase And Tensin Homolog (PTEN), which negatively regulates PI3K. Based on these data, the novel combination of selumetinib and AZD8186 may represent a new option for this subtype of PM, which has a worse prognosis (Marques et al., 2020).

7. Targeting VEGF/AXL axis

Vascular-Endothelial Growth Factor (VEGF) is a vital protein that supports the formation of blood vessels in normal and abnormal states. Tumor cells use VEGF to aid their survival and invasion (Goel and Mercurio, 2013). In patients with PM, due to elevated levels of VEGF detected, inhibitors of VEGF pathway have been tested as targeted treatment (Yasumitsu et al., 2010). Unfortunately, several studies examining the efficacy of angiogenic inhibitors alone, such as monoclonal antibodies and TKIs, in patients with PM, have shown mainly negative results. NVALT 5 trial, which compared thalidomide to active supportive care after first-line chemotherapy with cisplatin-pemetrexed in patients with PM, failed to demonstrate PFS benefit (Buikhuisen et al., 2013).

Indeed, the use of anti-angiogenic drugs has shown more promising results when combined with other standard treatment. In first line setting, the addiction of bevacizumab to platinum-pemetrexed chemotherapy has reported increase in PFS and OS in large phase III trial and could be considered as valid therapeutic option for treatment naïve PM patients, while other molecules such as nintedanib and ceridanib has shown conflicting results (Zalcman et al., 2016; Kindler et al., 2012; Scagliotti et al., 2019; Grosso et al., 2017; Tsao et al., 2019). Recently, another approached of combined treatment with ICI, chemotherapy and anti-angiogenic drugs has been evaluated in the BEAT-Meso trial. It is a randomized phase III trial whose primary endpoint is to assess difference in OS of carboplatin-pemetrexed-bevacizumab with or without atezolizumab, given as first line therapy. Despite an increase in PFS and a good safety profile of the combined ICI-chemo-bevacizumab arm, the study fails to demonstrate OS benefit in the overall population. However, as seen before with immunotherapy, this combination showed better survival outcomes in non-epiteliod histologies, suggesting a potential target for the treatment in this subgroup (Popat et al., 2024).

For pre-treated PM patients, different trials have evaluated the use of anti-angiogenesis TKIs, without any consistent results until now (Nowak et al., 2012; Jahan et al., 2012). The phase Ib PEMBIB trail, which evaluated the safety of nintedanib plus pembrolizumab in pretreated PM patients, has shown interesting activity data of this combinations (Danlos et al., 2023). Similarly, the angiogenic multikinase inhibitor Lenvatinib has been investigated in combination with pembrolizumab, demonstrating an ORR of 48 % (Douma et al., 2023). The RAMES trial, a randomized phase II trial evaluating gemcitabine-ramucirumab vs gemcitabine-placebo in pretreated patients with PM, has showed advantage in terms of OS in experimental arm (mOS 13.8 vs. 7.5 months; HR=0.71) (Pinto et al., 2021).

Another known contributing factor to angiogenesis in PM is AXL, a surface receptor tyrosine kinase, which is overexpressed in 74 % of cases and has potential therapeutic implications (Krebs et al., 2018). MiST-3, an ongoing phase II study, still recruiting (NCT03654833) is evaluating an AXL inhibitor, bemcentinib (BGB324), combined with the anti-PD 1 pembrolizumab, in patients with relapsed PM previously treated with cisplatin-pemetrexed (Krebs et al., 2018). An interesting perspective could be the possibility of using drugs inhibiting AXL-p53 pathways, that correlates with treatment's resistance (Song et al., 2020).

8. Targeting epigenetics

Epigenetic changes are a distinct mechanism of tumorigenesis from mutagenesis, including DNA methylation, histone PTMs, chromatin remodeling, histone variant exchange, and long non-coding RNA regulation. In PM, which has a low tumor mutation burden, epigenetic dysregulation may play a crucial role in carcinogenesis caused by asbestos exposure. Methylation profiles of cancer-related genes have been shown to distinguish malignant from non-malignant mesothelial cells, and the degree of asbestos exposure is associated with the number of epigenetic alterations (Christensen et al., n.d.; Goto et al., n.d.).

Studies have suggested that DNA methyltransferase enzymes (DNMTs) and enhancer of zeste homolog 2 (EZH2) could be attractive targets for PM therapy. However, clinical trials using DNMT inhibitors have not shown promising results due to toxicities (Vogelzang et al., 1997). Tazemetostat, a selective oral inhibitor of histone methyltransferase, has shown efficacy in patients with BAP1 loss in a phase 2 trial (Zauderer et al., 2022). Similarly, Vorinostat, an oral drug histone deacetylase inhibitor (HDACi) has been tested in a phase I trial and demonstrated a stabilization of disease in 30 % (4 of 13) patients (Kelly et al., 2005). These findings led to accelerated clinical development of the drug and design of the phase III trial VANTAGE-014 (Krug et al., 2015). The study failed to demonstrate any advantage versus placebo as second or third line of treatment for unresectable PM in term of efficacy - mOS 30.7 weeks for vorinostat (95 % CI 26.7 – 36.1) vs 27.1 weeks (23.1 – 31.9) for placebo. Fatigue was reported as the most frequent grade 3 or worse adverse event in the experimental arm (51 [16 %] vs 25 [8 %] in the placebo group]) (Krug et al., 2015). Additionally, the immunomodulatory potential of epigenetic drugs is being investigated. Epigenetic drugs are able to influence both cancer cells and tumor microenvironment by modifying antigenic protein expression (Chiappinelli et al., 2016; Li et al., 2014) and antigen presentation (such as upregulation of MHC class I antigens and other components of the antigen processing machinery) (Campoli and Ferrone, 2008; Sigalotti et al., 2014; Adair and Hogan, 2009; Kitamura et al., 2007; Magner et al., 2000; Bukur et al., 2012; Dunn and Rao, 2017). These drugs could also modulate immune checkpoint proteins like CTLA-4, PD-1, PD-L1 and costimulatory molecules on cell lines (Dunn and Rao, 2017), impacting tumor-infiltrating lymphocytes. Epigenetic therapies can alter host immune cells, affecting NK cell activity (Zhu et al., 2015), MDSC

accumulation (Wang et al., 2017), and Treg function (Morikawa and Sakaguchi, 2014) and chemokine expression (Peng et al., 2015). Thus, they are able to enhance immune recognition and potentially reversing immune evasion. These insights suggest epigenetic modifications as potential biomarkers and targets to enhance the efficacy of ICI, particularly in mesothelioma and other cancers.

9. Targeting mesothelin

Mesothelin (MSLN) is a glycoprotein expressed on normal mesothelial cells and overexpressed in various types of cancers, including PM, where it plays a role in tumor invasion and malignant transformation (Hassan et al., 2016). The promoter methylation of *MSLN* and its low mRNA expression has been identified as a marker for sarcomatoid PM, a subset of the disease with a poor prognosis (Hmeljak et al., 2018). MSLN has been identified as a possible target for new therapeutic strategies for PM, and several clinical trials have been conducted with MSLN-targeted therapies. These include immunotoxins, antibody-drug conjugates, and cellular therapies (Popat et al., 2022).

SS1P is a recombinant immunotoxin with a murine anti-MSLN variable antibody fragment (Fv) and a Pseudomonas exotoxin A (PE) payload. It has been tested as a single agent in patients with MSLN-expressing PM, ovarian, and pancreatic cancer (Chowdhury et al., 1998; Pastan et al., 2006; Hassan et al., 2007). SS1P has also been tested in combination with cisplatin and pemetrexed in a phase I trial involving therapy-naïve epithelial or biphasic PM patients (Hassan et al., 2014). A pilot phase I/II study of pentostatin plus cyclophosphamide immune depletion in combination with SS1P was conducted to decrease immunogenicity of the immunotoxin (Anon, n.d.). This approach delayed the development of neutralizing antibodies to SS1P and allowed multiple cycles of therapy (Hassan et al., 2013). Despite positive results in terms of response, no clinical trials with SS1P in PM are currently active, and attention has shifted to less immunogenic anti-MSLN immunotoxins. LMB-100 (RG7787) is a humanized anti-MSLN Fab fragment with a newly designed PE payload engineered to be less immunogenic than SS1P and to have decreased toxicity in animal models (Hassan et al., 2016; Alewine et al., 2014). A phase I trial of intratumor injection of LMB-100, in combination with ipilimumab is ongoing (Anon, n.d.).

Anetumab ravtansine is an antibody-drug conjugate comprising a fully human IgG1 anti-MSLN monoclonal antibody conjugated to the maytansine derivative tubulin inhibitor DM4, which shows highly selective killing activity on MSLN-expressing tumor cells compared with MSLN-negative cells (Golfier et al., 2014). Clinical trials have been conducted for anetumab ravtansine alone in PM and ovarian cancer patients. The most frequent drug-related adverse events (AEs) of any grade were fatigue, nausea, diarrhea, anorexia, vomiting, and peripheral sensory neuropathy, and the most frequent grade 3 or higher drug-related AEs were fatigue, keratitis/keratopathy, and nausea. Overall, of the 138 patients evaluable for response, 66 patients had stable disease, 11 patients had partial and 1 complete responses (Hassan et al., 2020). This encouraging data led to the start of the ARCS-M trial, a randomized phase II study comparing anetumab ravtansine to vinorelbine in relapsed PM patients with MSLN-positive tumors. The trial enrolled 248 patients, randomly assigned to the two treatment groups, with 166 patients receiving anetumab ravtansine and 82 receiving vinorelbine. However, the trial did not show superiority of anetumab ravtansine over vinorelbine, with a median PFS of 4.3 months (95 % CI 4.1–5.2) with the experimental drug compared to 4.5 months (95 % CI 4.1–5.8) with vinorelbine (HR 1.22, 95 % CI 0.85–1.74, log-rank p=0.86) (Kindler et al., 2022).

Two phase I/II trials of novel MSLN-targeting cell therapies are currently recruiting, including gavocabtagene autoleucel (gavo-cel; TC-210) and TC-510 (Anon, n.d.; Anon, n.d.). TC-210 is an autologous genetically engineered T cell therapy that expresses a single-domain antibody recognizing MSLN, fused to the CD3-epsilon subunit, and preliminary results showed promising outcomes in 17 patients (12 with PM) (Hong et al., 2021). TC-510, on the other hand, comprises autologous genetically engineered T cells expressing two synthetic constructs, a single-domain antibody recognizing human MSLN fused to the CD3-epsilon subunit, and a PD-1:CD28 switch receptor. In addition, two phase I CAR-T trials targeting MSLN are ongoing: NCT03054298, investigating lentiviral transduced huCART-meso cells, and NCT04489862, evaluating the safety and tolerability of autologous MSLN-targeted CAR-T cells secreting PD-1 nanobodies (αPD1-MSLN-CAR T cells) (Anon, n.d.; Anon, n.d.)

10. Discussion

The intricate landscape of PM indeed necessitates a nuanced approach to therapeutic interventions. The exploration of various molecular pathways and targeted therapies underscores the complexity inherent in this disease. While traditional platinum-based chemotherapy has been a mainstay, the advent of ICIs has ushered in a new era, as demonstrated by the landmark Checkmate 743 trial, highlighting the efficacy of nivolumab plus ipilimumab over chemotherapy, particularly for non-epithelioid tumors. However, challenges persist, notably stemming from the heterogeneity within and between patients and the absence of specific biomarkers.

Targeted treatments addressing genotypic and phenotypic alterations could present a viable approach for PM, thereby promoting precision oncology in this rare disease and offering patients new therapeutic options. Through the study of genetic alterations, it is evident that single-gene mutations or rearrangements are rare in PM. Furthermore, the use of specific TKIs to develop a target approach has yielded mixed results, emphasizing the need for a suppressing signaling pathway strategy that targets the most deregulated pathways in PM (Baas et al., 2021; Cao et al., 2014; Fennell et al., 2022; Hiltbrunner et al., 2022; Hmeljak et al., 2018; Perera and Mansfield, 2022; Sekido, 2010; Terenziani et al., 2022; Zhang et al., 2013; Aliagas et al., 2021).

Notably, the frequent deletion of the *CDKN2A* gene, occurring in approximately 70 % of PM cases, stands out as a significant genomic alteration linked to poor prognosis (Cao et al., 2014; Bueno et al., 2016). While the promising results of CDK4/6 inhibitors, particularly abemaciclib, in p16INK4A-negative PM are noteworthy, it is crucial to critically assess the response variability among patients. Acknowledging the impact of patient heterogeneity on the effectiveness of CDK4/6 inhibitors, especially concerning the status of *CDKN2A*, will contribute to a more nuanced understanding of this therapeutic approach. *CDKN2A* loss may find successful targeting through CDK4/6 inhibitors, especially when combined with chemotherapy, particularly for PM patients with an immune "cold" microenvironment post ICI failure.

Other distinct molecular profiles within PM that may suggest tailored approaches could be found in defects in MMR genes, that may benefit from ICI, and in HR pathway, such as BAP1, which result in susceptibility to PARP inhibitors (Parrotta et al., 2017). However, the role of these alterations in enhancing ICI response in PM necessitates further exploration.

Of note, the Hippo pathway, given its intricate involvement in cellular processes and its dysregulation in PM, particularly through the loss of function of NF2, holds promise as a potential therapeutic target (Cerami et al., 2012; Gao et al., 2013). Strategies targeting Hippo alterations include FAK inhibitors, such as GSK2256098, showing clinical promise. Additionally, CUL4, stimulated by neddylation in NF2-loss PM, presents a potential target with pevonedistat. Promisingly, molecules targeting TEAD are in phase I trials (Anon, n.d; Anon, n.d; Anon, n.d).

The exploration of anti-angiogenic therapies in PM brings up a multifaceted landscape marked by both promising advancements and persistent challenges. The encouraging outcome of the phase III MAPS trial, revealing enhanced OS with the incorporation of bevacizumab into the conventional regimen, has underscored the potential of VEGF pathway inhibition. However, the narrative takes a turn when confronted with the divergent outcomes reported in first-line studies

investigating anti-angiogenic drugs. Exploration of angiogenic inhibition strategies continues through ongoing trials examining the role of anti-VEGF/VEGFR drugs and AXL inhibitors in combination with ICI, holding the potential for promising results (Krebs et al., 2018; Anon, n.d.). Epigenetic alterations emerge as key players in PM tumorigenesis, propelled by asbestos exposure. This paradigm shift, acknowledging the low tumor mutation burden in PM, underscores the centrality of epigenetic dysregulation in the context of this malignancy. DNMT and Histone methyltransferase inhibitors have shown some response data, although unexpected toxicities have interrupted their development (Kelly et al., 2005; Vogelzang et al., 1997; Zauderer et al., 2022). These findings necessitate a meticulous examination of the risk-benefit profile, urging the oncology community to recalibrate expectations and refine strategies. Currently, MSLN emerges as the most promising target for new therapeutic strategies, with ongoing clinical trials exploring less immunogenic immunotoxins, autologous genetically engineered T cells, and CAR-T (Anon, n.d.; Hong et al., 2021; Anon, n.d., Anon, n.d.).

While these approaches show potential, it is also important to recognize that PM biology is complex, and targeting a single pathway may not be sufficient in all cases. This heterogeneity in responses emphasizes the pressing need for precision medicine paradigms, where therapeutic decisions are guided by the unique molecular landscape of individual tumors. Challenges include the need for innovative trial designs, identifying reliable biomarkers and consideration of patient heterogeneity, emphasizing the intricate landscape of PM therapeutics. The road to implementing targeted approaches in PM clinical practice is not without challenges. Precise patient selection based on genomic profiling and molecular characterization is imperative, necessitating collaborative efforts between oncologists and molecular pathologists. The multifaceted nature of PM underscores the need for strategic planning in combination therapies, posing challenges in managing potential side effects and determining optimal sequencing. Identifying reliable biomarkers and developing predictive tests for targeted therapies remains a critical ongoing research frontier. Innovative clinical trial designs, such as basket and umbrella trials, accommodating molecular subtypes, could provide a robust platform for testing targeted therapies. Yet, ethical concerns regarding the cost of targeted therapies and ensuring patient access persist. Collaborative efforts involving pharmaceutical companies and health systems are pivotal to address these issues.

In conclusion, while challenges are evident, the evolving understanding of PM's molecular landscape offers a myriad of promising targeted approaches. The path forward involves a harmonious blend of these approaches, guided by molecular profiling and innovative trial designs. Collaboration among researchers, clinicians, and pharmaceutical partners is key to transforming these promising strategies into impactful clinical interventions. The era of personalized and precision medicine for PM is within reach, and overcoming these challenges will pave the way for its successful implementation.

Disclosure

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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