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# Recent advances in therapeutic strategies for malignant pleural mesothelioma: An integrative review

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## Abstract

**Background:** Malignant pleural mesothelioma (MPM) is an aggressive malignancy of the pleural mesothelium primarily associated with asbestos exposure. Traditional management with chemotherapy and surgery provides limited survival benefits. However, advances in molecular profiling and immunotherapy have redefined therapeutic strategies in recent years.

**Methods:** This review integrates recent preclinical and clinical evidence from 27 key publications addressing immune checkpoint inhibitors, targeted therapies, and diagnostic biomarkers. Emphasis was placed on molecular mechanisms—including AXL–ATR, PI3K/AKT/mTOR, Hippo–YAP/TAZ, and CD26–SSTR4 pathways—and their translation into clinical practice.

**Results:** Combination regimens incorporating immunotherapy, angiogenesis inhibition, and DNA damage repair blockade have shown synergistic potential. Novel antibody- based therapies, particularly anti-CD10 and anti-CD26, have demonstrated promising preclinical efficacy. Molecular characterization of BAP1, NF2, and CDKN2A has refined diagnostic reproducibility.

**Conclusions:** Integration of immunotherapy and molecularly targeted approaches, guided by genomic and transcriptomic profiling, is transforming MPM treatment. Continued development of antibody-based and omics-driven precision therapies will be essential to improving outcomes in this previously intractable disease.

***Keywords:*** Malignant pleural mesothelioma; Immunotherapy; Targeted therapy; Molecular profiling; AXL–ATR pathway; CD26; CD10; BAP1; NF2; Precision medicine; Antibody- based therapy; Omics-driven oncology.

## Introduction

Malignant pleural mesothelioma (MPM) is a rare but highly aggressive neoplasm associated with chronic asbestos exposure, accounting for approximately 80 percent of cases. It is classified into epithelioid, sarcomatoid, and biphasic subtypes, each with distinct prognoses and therapeutic responses. Conventional treatment combining platinum and pemetrexed remains the standard of care, yet median survival seldom exceeds 18 months. In recent years, extensive translational studies and comprehensive reviews have highlighted a dramatic shift in therapeutic paradigms [1-3]. Genomic and transcriptomic profiling has revealed recurrent mutations in BAP1, NF2, and CDKN2A, as well as dysregulation of the PI3K/AKT/mTOR and Hippo–YAP/TAZ pathways [4-6]. These studies, including early gene expression profiling by Pass et al [5], have provided a rationale for biomarker-based and targeted therapy strategies [7].

### Conventional and Anti-Angiogenic Therapies

The historical backbone of systemic therapy for MPM remains the cisplatin–pemetrexed doublet. Attempts to enhance efficacy led to the MAPS trial, demonstrating that the addition of bevacizumab improved overall survival from 16.1 to 18.8 months [8]. Similarly, the RAMES trial reported benefits with ramucirumab in second-line settings, supporting the anti-angiogenic approach [9]. Nevertheless, chemotherapy resistance and limited durability of responses have driven exploration of alternative modalities, including immunotherapy and targeted treatment combinations [10,11]. Current ESMO [8] and NCCN [12] guidelines advocate for a multimodal approach integrating systemic and surgical strategies [13].

### Immunotherapy and checkpoint inhibition

The most significant progress in recent years has been the introduction of immune checkpoint inhibitors (ICIs). The phase III CheckMate-743 trial showed that dual blockade with nivolumab and ipilimumab significantly prolonged survival compared to chemotherapy alone [14]. Single-agent ICIs, such as durvalumab or pembrolizumab, have demonstrated activity in selected patients with high PD-L1 expression. Early phase studies (DREAM, NIBIT-MESO-1) revealed synergistic effects when ICIs were combined with chemotherapy or anti-angiogenic therapy [15,16]. Despite these successes, resistance mechanisms, including immunosuppressive microenvironment and defective antigen presentation, remain challenges. Current trials are exploring strategies integrating PARP/ATR inhibitors and oncolytic viral therapies to enhance response durability [7].

### Molecular targeted therapies

The identification of molecular drivers has opened new therapeutic avenues for MPM. Among these, the AXL–ATR axis has emerged as a promising target. Dual inhibition of AXL and ATR signaling was shown to impair DNA-damage repair and induce apoptosis in BAP1-deficient cells [7,17]. The PI3K/AKT/mTOR pathway, frequently activated following NF2 loss, also contributes to mesothelial proliferation and immune evasion. The Hippo–YAP/TAZ pathway—a hallmark of NF2 inactivation—plays a crucial role in maintaining stemness and tumor progression. Agents such as verteporfin and TEAD inhibitors are under investigation for suppressing this pathway. Additionally, the CD26–SSTR4 axis represents an emerging immunoregulatory target.

**Table 1:** Major clinical trials and outcomes in malignant pleural mesothelioma.

| Study | Therapy | Key findings | Reference |
|---|---|---|---|
| MAPS Trial | Cisplatin + Pemetrexed ± Bevacizumab | Improved OS (18.8 vs 16.1 months) | Int J Mol Sci, 2023 |
| RAMES | Gemcitabine + Ramucirumab | Extended OS (13.8 vs 7.5 months) | Front Pharmacol, 2021 |
| Check-Mate-743 | Nivolumab + Ipilimumab | Superior OS vs chemo; durable benefit | N Engl J Med, 2021 |
| DREAM | Durvalumab + Cisplatin + Pemetrexed | Improved PFS; manageable irAEs | Clin Cancer Res, 2020 |
| NIBIT-MESO-1 | Tremelimumab + Durvalumab | High disease control rate | J Thorac Oncol, 2020 |
| AXL–ATR Study | AXL & ATR inhibitors | Synergistic DNA damage and apoptosis | Mol Cancer Ther, 2024 |
| CD26–SSTR4 Axis | CD26 modulation (monoclonal antibody/analog) | Growth inhibition; apoptosis induction | Br J Cancer, 2014 |

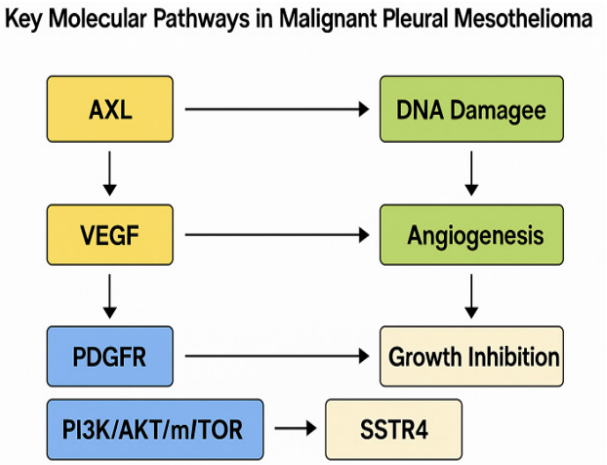


**Figure 1:** Molecular Pathways in Malignant Pleural Mesothelioma.

In vitro and in vivo models have demonstrated that anti-CD26 monoclonal antibodies suppress MPM growth by modulating SSTR4-mediated signaling [6,18,19].

Figure 1 shows the major molecular pathways in malignant pleural mesothelioma. Schematic representation of AXL–ATR, VEGF–VEGFR, PI3K/AKT/mTOR, Hippo–YAP/TAZ, and CD26–SSTR4 pathways involved in tumor proliferation, angiogenesis, and immune modulation. Beyond its antitumor role, CD26/DP-PIV exerts multiple biological functions in immune regulation, cytokine processing, and signal transduction, underscoring its therapeutic potential across cancer types.

### Genomic and transcriptomic insights

Comprehensive genomic profiling has revealed MPM as a genetically heterogeneous disease. Frequent mutations in BAP1, CDKN2A, and NF2 drive tumor initiation and progression [4,5]. Transcriptomic studies by Crispi et al identified gene expression signatures associated with aggressive phenotypes and potential biomarkers for targeted therapy [6]. Similarly, large-scale

**Table 2:** Histologic and molecular markers for the diagnosis and classification of malignant pleural mesothelioma.

| Category | Marker/Gene | Function or diagnostic utility | Clinical implication / Notes |
|---|---|---|---|
| Histologic markers | Calretinin | Calcium-binding protein expressed in mesothelial cells | Positive in MPM; distinguishes from adenocarcinoma |
| | WT1 | Nuclear transcription factor | Highly specific for mesothelial origin |
| | Cytokeratin 5/6 | Intermediate filament protein | Supports mesothelial differentiation |
| | D2-40 (podoplanin) | Lymphatic endothelial marker | Positive in MPM; negative in carcinoma |
| Loss-of-function markers | BAP1 | Tumor suppressor involved in DNA repair | Nuclear loss supports malignancy; predicts response to PARP inhibitors |
| | MTAP | Enzyme linked to CDKN2A region on 9p21 | Loss correlates with CDKN2A deletion; surrogate IHC marker |
| Genetic alterations | CDKN2A (p16) | Cell-cycle regulator | Homozygous deletion detected by FISH confirms malignancy |
| | NF2 | Hippo pathway regulator | Loss activates YAP/TAZ; potential target for TEAD inhibitors |
| | BAP1/NF2 co-loss | Combined genomic signature | Defines distinct molecular subset with poor prognosis |
| Immunologic markers | PD-L1 | Immune checkpoint ligand | Expression predicts response to ICI therapy |
| | CD26 (SSTR4 axis) | Cell-surface glycoprotein / serine protease | Diagnostic and therapeutic target; basis for anti-CD26 therapy |
| Emerging biomarkers | Mesothelin | Membrane glycoprotein | Serum and pleural fluid marker for diagnosis and monitoring |
| | Fibulin-3 | Extracellular matrix protein | May improve early diagnosis when combined with mesothelin |
| | MTAP + BAP1 panel | Combined IHC test | Enhances specificity for MPM vs reactive mesothelial proliferation |

profiling by Hmeljak et al. and Bueno et al. demonstrated that transcriptomic subgroups correlate with clinical outcomes, highlighting the potential of precision stratification based on immune and angiogenic activity [21,22]. These findings collectively emphasize the need for integrated genomic– transcriptomic diagnostics to guide therapy selection and predict prognosis.

### Diagnostic and pathological advances

Accurate diagnosis and grading of MPM have improved through integration of morphologic and molecular data. The WHO 2021 classification introduced a three-tiered grading system based on nuclear atypia, mitotic activity, and necrosis [23,24]. Immunohistochemical markers such as BAP1, MTAP, WT1, and calretinin aid differentiation from benign mesothelial proliferations. Homozygous deletion of CDKN2A detected by FISH confirms malignancy, while BAP1 loss indicates susceptibility to DNA-damage repair–targeting therapies [25].

Table 2 summarizes WHO 2021 histologic criteria and associated immunohistochemical/genetic markers (BAP1, MTAP, WT1, CDKN2A, PD-L1, and CD26/SSTR4).

Integration of digital pathology and AI-based image analysis enhances reproducibility and enables semi-automated grading systems. Combined with molecular assays, these approaches underpin a move toward personalized histopathologic diagnostics.

### Future perspectives

Recent reviews have underscored the momentum toward multimodal and personalized strategies [26]. Combination regimens incorporating ICIs with anti- angiogenic agents, PARP/ATR inhibitors, or epigenetic modulators are under active investigation [15,16,26]. Emerging cell-based therapies, including CAR-T and dendritic cell vaccines, demonstrate promising safety and early efficacy signals. International guidelines now recommend molecular testing for BAP1, NF2, and CDKN2A as part of 3 clinical decision-making [13]. Pan K and Mizutani et al. antibody studies targeting CD10 and CD26 provide new avenues for monoclonal antibody–based therapies [18,19,20]. As translational research accelerates, the integration of omics-driven biomarkers and immune–molecular synergy will likely define the next phase of MPM management. Emerging immune and inflammatory biomarkers, such as the Mesothelioma Systemic Inflammation Score, may help predict response to multimodal therapies and guide individualized treatment strategies [27].

## Conclusions

MPM remains one of the most challenging malignancies in thoracic oncology. Despite historical therapeutic stagnation, the integration of molecular diagnostics, immune checkpoint inhibition, and targeted therapies has redefined the treatment landscape. Genomic insights into BAP1, NF2, CDKN2A, and TERT mutations now support individualized therapy selection. Advances in antibody-based therapeutics, such as those targeting CD10 and CD26, illustrate the expanding role of biologics in MPM management [18,19]. Multimodal approaches combining immunotherapy, angiogenesis inhibition, and DNA-damage repair blockade represent the future of care. Recent comprehensive reviews and guidelines emphasize the transition toward omics-driven and immune- integrated treatment frameworks [26,28]. Ultimately, translating molecular and immunologic discoveries into clinical practice will be the key to improving outcomes in this historically intractable disease.

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