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# The past, present, and future of targeted therapeutic approaches in patients with diffuse pleural mesotheliomas

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## Abstract

Despite our growing understanding of the genomic landscape of diffuse pleural mesotheliomas (DPM), there has been limited success in targeted therapeutic strategies for the disease. This review summarizes attempts to develop targeted therapies in DPM, focusing on the following targets being clinically explored in recent and ongoing clinical trials: vascular endothelial growth factor, mesothelin, BRCA1-associated protein 1, Wilms tumor 1 protein, NF2/YAP/TAZ, CDKN2, methylthioadenosine phosphorylase, v-domain Ig suppressor T-cell activation, and argininosuccinate synthetase 1. Although preclinical data for these targets are promising, few have efficaciously translated to benefit our patients. Future efforts should seek to expand the availability of preclinical models that faithfully recapitulate DPM biology, develop clinically relevant biomarkers, and refine patient selection criteria for clinical trials.

**Keywords:** Mesothelioma, targeted therapy, biomarkers, genomics

## INTRODUCTION

Diffuse pleural mesothelioma (DPM) is an aggressive malignancy of the mesothelial lining of the pleural cavity with unacceptably poor outcomes, with less than 10% of patients surviving past 5 years[1]. Approximately 3,300 patients are diagnosed annually with DPM in the United States, and globally, the incidence continues to rise in association with asbestos exposure[2-5]. Despite recent advances, DPM remains a recalcitrant disease, with even patients with early-stage disease having a high rate of recurrence despite aggressive multimodality therapy[6,7].

DPM has been the subject of extensive genomic analyses making it a rich field for the pursuit of targeted therapy. Whole exome sequencing of malignant mesotheliomas identifies significant mutational burdens in *BAP1, NF2, TP53,* and *SETD2*, amongst many others[8]. In addition to this extensive genomic profiling, immunohistochemistry (IHC) has confirmed protein targets for investigation, such as WT1[9,10], mesothelin[11,12], BAP1[13-15], and VISTA[16,17] and histologic subtype has shown both prognostic and possibly predictive implications[18]. As we gain further insights into the molecular landscape of mesothelioma, there is hope that targeted therapeutic strategies akin to those seen in non-small cell lung cancers over the past two decades will soon follow[19].

However, despite the myriad of efforts to drug these promising targets, in 2022, there exists not a single FDA-approved targeted therapy for patients with DPM. Unresectable/metastatic DPM is traditionally treated with systemic therapies. There are currently only two approved options for patients with DPM, both of which are in the first-line (1L) setting: platinum doublet chemotherapy[20] and combination immune checkpoint inhibitor (ICI) therapy with ipilimumab and nivolumab[18]. Both regimens are biomarker agnostic, with the latter showing preferential benefit in non-epithelioid histology (biphasic and sarcomatoid) but remaining an option for all histologic subtypes. There are currently no approved treatment options for patients after progression on 1L therapy.

With our growing understanding of the genomic landscape of mesotheliomas[8,16,21,22], the field is focused on integrating these findings into the care of our patients. Efforts to comprehensively integrate next-generation sequencing (NGS) findings as a prognosticator for patients with mesothelioma are ongoing, typified by the recently published Oncocast-MPM, an open-source, web-accessible, machine-learning risk-prediction model incorporating genomic profiling from patients with DPM which was validated to provide more comprehensive prognostication[22]. At present, there are no approved nor recommended, genomically defined targeted therapies for patients with DPM. Targeted strategies are, at times, used off-label in the proper clinical settings, including in those rare mesotheliomas harboring *ALK* rearrangements[23-25], *NTRK* fusions[26], and *BRAF* V600E[27] mutations. These approaches have not been systematically evaluated as therapeutic drug targets in mesothelioma, and the use of targeted medications for these indications is extrapolated from data in other malignancies[28]. Further exploration of predictive markers and their actionability is needed.

In this review, we will focus on oncogenic targets under active clinical investigation for patients with DPM [Figure 1].

## THERAPEUTIC TARGETS OF INTEREST

***Vascular endothelial growth factor (VEGF):*** activation of VEGF and its signaling cascade is critical for tumorigenesis and cell survival[29] across solid tumor types. Inhibition of VEGF signaling has been extensively studied in DPM and is accomplished using targeted antibodies or VEGF tyrosine kinase inhibitors (TKIs). Evidence supporting the use of VEGF inhibitors in DPM has led to their incorporation into National Comprehensive Cancer Network (NCCN) guideline recommendations[30].

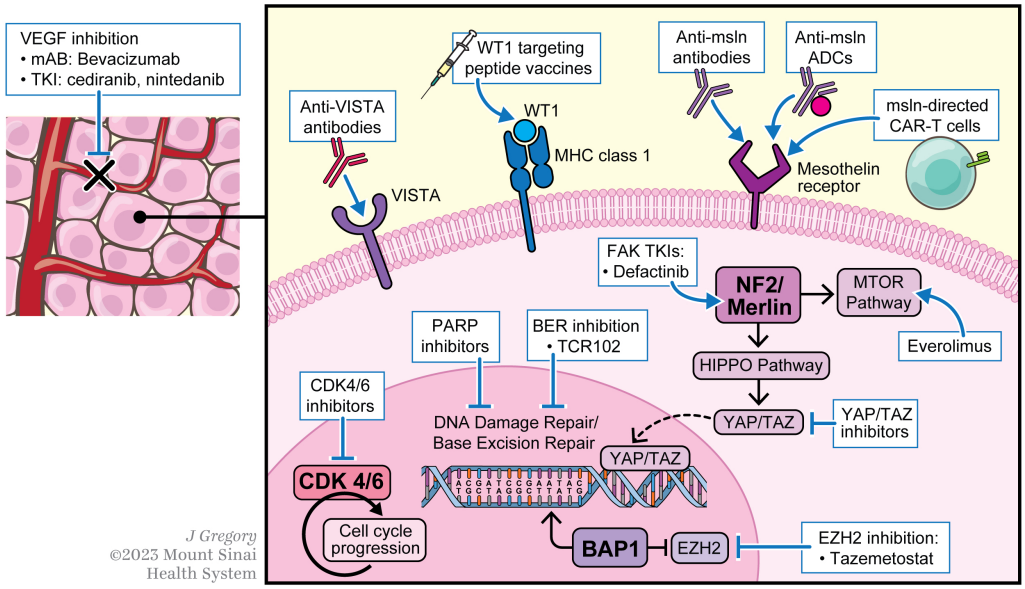


**Figure 1.** Graphical abstract illustrating the targets of interest described. mAB: Monoclonal antibody; TKI: tyrosine kinase inhibitor; msln: mesothelin; ADC: antibody-drug conjugate.

*VEGF inhibitory (VEGFi) antibodies*. The phase 3 MAPS trial randomized 448 patients with DPM to receive cisplatin and pemetrexed with or without the anti-VEGF-A antibody bevacizumab[31]. In this study, median overall survival (OS) was significantly longer in the bevacizumab combination arm (18.8 *vs.* 16.1 months, HR 0.77, [95%CI: 0.62-0.95], $P = 0.02$), leading to the inclusion of the triplet therapy regimen in guidelines for 1L recommended treatments in advanced DPM[30,32]. The MAPS trial predates the integration of 1L ipilimumab and nivolumab as a treatment option for patients with DPM and bevacizumab was not allowed in the comparison arm of the CheckMate 743 trial[18]. As such, a direct comparison of platinum/pemetrexed/bevacizumab to dual checkpoint blockade cannot be made. With the integration of immunotherapy into routine practice and the availability of data suggesting an immunomodulatory benefit of VEGFi antibodies with ICI[33], the role of VEGFi antibodies in the 1L setting needs to be re-explored. To that end, the MAPS regimen is currently under investigation in combination with ICI in the 1L phase 3 BEAT-meso trial (NCT03762018) evaluating, in a 1:1 randomization, platinum, pemetrexed, bevacizumab with or without atezolizumab.

Given evolving 1L treatment options in DPM, there is a need to evaluate the utility of VEGFi antibodies in later lines of treatment. The recent double-blind, multicenter, randomized phase 2 RAMES trial examined the inclusion of the anti-VEGFR-2 antibody, ramucirumab, with a standard later-line chemotherapy option, gemcitabine. The study randomized 161 patients to receive gemcitabine with either placebo or ramucirumab. Median OS was significantly longer in the gemcitabine + ramucirumab arm (13.8 *vs.* 7.5 months, HR 0.71 [95%CI: 0.59-0.85], $P = 0.03$)[34]. A phase 2 trial of atezolizumab and bevacizumab in the later-line setting for patients with peritoneal mesothelioma, a clinically[35] and genomically[21,36] distinct malignancy of the abdominal cavity, found a promising response rate of 40% with a median duration of response of 12.8 months[37]. These trials lend credence to the argument that VEGF inhibitors are effective treatment options for patients with mesotheliomas. With the movement of ICI into the 1L setting for some patients, it is difficult to know where to incorporate these agents, and in what combinations, without further prospective studies.

*VEGF TKIs.* In contrast to VEGFi antibodies, VEGF TKIs have failed to demonstrate improved efficacy compared to standard-of-care regimens [Table 1]. The 1L phase 2 SWOG S0905 trial of cediranib (TKI with activity against VEGF and PDGFR) with cisplatin and pemetrexed did not show significant clinical efficacy over chemotherapy alone[38,39] and the phase 2 trial of cediranib monotherapy in patients with ≤ 1 prior line of treatment showed modest clinical benefit but at an intolerable dose level[40]. The 1L phase 3 LUME-Meso trial of cisplatin/pemetrexed with nintedanib (a multi-kinase TKI with activity against PDFG, FGF2, TGFβ, and VEGF) failed to show significant clinical benefit compared to chemotherapy[41], and the phase 2 trial of nintedanib in previously treated patients with DPM did not meet its prespecified progression-free survival (PFS) endpoint[42]. To date, there are no approved nor recommended VEGF TKIs for patients with DPM.

***Mesothelin:*** Mesothelin (MSLN) is a membrane-anchored cell surface glycoprotein that is highly expressed in several solid tumors including DPM[11,43]. In preclinical models, MSLN overexpression promotes tumorigenesis and tumor invasion[12,44]. Over the last several decades, there have been several attempts to therapeutically exploit the overexpression of MSLN in DPM using multiple novel constructs, including antibody-drug conjugates (ADCs), immunotoxins, and adoptive cellular therapies[45].

*Mesothelin Antibodies.* Trials of MSLN targeting antibodies have produced mixed results. The chimeric, humanized IgG1 monoclonal antibody amatuximab was evaluated in a phase 2, single-arm trial in DPM, where it was combined with cisplatin and pemetrexed for six cycles, followed by maintenance amatuximab until disease progression. While the combination was found to be tolerable, the primary endpoint of PFS was not improved in the treatment arm compared to chemotherapy alone, and the construct has not progressed to a phase 3 investigation[46].

SS1P is a mesothelin-targeting antibody attached to a truncated fragment of Pseudomonas exotoxin A. With preclinical data suggesting pseudomonas exotoxin A induces immunogenic cell death in DPM[47], there was a rationale to test whether SS1P could lead to a tolerable therapeutic index and efficacy signal in DPM. The drug was evaluated in a phase 1 trial in combination with cisplatin and pemetrexed for 1L treatment of DPM[48]. In 20 evaluable patients, there was an initial efficacy signal with an overall response rate of 60%; however, neutralizing antidrug antibody formation within the first cycle limited its initial clinical development in DPM. Lymphodepleting regimens (pentostatin/cyclophosphamide) to delay antidrug antibody formation showed some early promise[49] but, at present, are not being actively investigated in larger prospective trials for DPM.

A second-generation immunotoxin, LMB-100, was subsequently designed to be less immunogenic than SS1P[50] to avoid the development of neutralizing antibodies, which were thought to limit single-agent activity. A phase I trial of LMB-100 in advanced MSLN-expressing cancers found that the drug was indeed less immunogenic. However, most patients developed antidrug antibodies after two cycles of the drug, prompting the researchers to conclude that this formulation would have similarly limited single-agent activity as SS1P[51]. While a planned phase II study examining LMB-100 in combination with pembrolizumab (NCT03644550) in the later-line setting was withdrawn due to the evolving 1L landscape after the integration of CheckMate743, a study evaluating the role of normothermic intrapleural LMB-100 after cytoreductive surgery (NCT0537825) is soon to open.

Under the current investigation is the novel MSLN-directed protein construct HPN536. HPN536 is a T-cell-activating protein-based construct targeting MSLN-expressing tumor cells and engaging CD3ε on T cells via an albumin linker. HPN536 tethers T cells and MSLN-expressing target cells together, enabling the formation of a cytolytic synapse resulting in T cell-dependent cellular cytotoxicity (TDCC) with preclinical

**Table 1. VEGF TKIs in mesothelioma**

| NCT ID | Phase | Product | Target patient population | Outcomes | Reference |
|---|---|---|---|---|---|
| NCT01064648 | 2 | Cisplatin/pemetrexed +/- cediranib | 92 patients with treatment naïve unresectable DPM | Combination *vs.* chemotherapy alone: PFS: 6.9 *vs.* 5.6 months (HR 0.77, 95%CI: 0.59-1.02); OS: 10.0 *vs.* 8.5 months (HR 0.88, 95%CI: 0.65-1.17) | [38,39] |
| NCT00309946 | 2 | Cediranib | 51 patients with DPM and ≤ 1 prior line of therapy | PFS: 1.8 months, OS: 4.4 months. 45 mg dose level improved response rate but intolerable toxicity | [40] |
| NCT01907100 | 3 | Cisplatin/pemetrexed +/- nintedanib | 458 treatment naïve patients with DPM randomized 1:1 to chemotherapy alone and combination | Combination *vs.* chemotherapy alone: PFS: 6.8 *vs.* 7.0 months (HR 1.01, 95%CI: 0.79-1.30) | [41] |
| NCT02568449 | 2 | Nintedanib | 20 patients with DPM who previously received chemotherapy | PFS: 1.8 months; OS: 4.2 months | [42] |

DPM: Diffuse pleural mesothelioma; PFS: progression-free survival; OS: overall survival; HR: hazards ratio; CI: confidence interval.

models demonstrating increased cell death and tumor growth inhibition[52]. A phase I trial investigating the safety and recommended phase 2 dose (RP2D) of this drug in MSLN-expressing advanced tumors, including DPM, is open but closed to recruitment (NCT03872206).

*Mesothelin Antibody-Drug Conjugate (ADC).* Anetumab ravtansine is an ADC comprised of an IgG1 anti-MSLN antibody conjugated to the maytansine derivative tubulin inhibitor DM4 via a reducible disulfide linker. The payload induces cell cycle arrest and apoptosis and has significant antitumor activity in preclinical xenograft mesothelioma models[53]. The initial phase 1 trial noted a promising preliminary partial response rate of 31%[54], prompting the randomized phase II ARCS-M trial examining anetumab ravtansine for the treatment of mesothelin-positive DPM. The trial randomly assigned 248 patients whose disease had progressed on prior platinum/pemetrexed with or without bevacizumab to receive anetumab ravtansine or vinorelbine. Unfortunately, the primary endpoint of PFS was no better with anetumab ravtansine than vinorelbine and there was no significant difference in OS between the groups [Table 2][55]. This large negative prospective trial highlights the importance of further refining biomarker development and mesothelin-ADCs in DPM to better characterize those most likely to benefit[57]. Another phase I/2a mesothelin-ADC clinical trial, BMS-986148, was recently published, showing an acceptable safety profile and a modest signal of clinical benefit in patients with DPM, particularly when used in combination with nivolumab (NCT02341625; Table 2)[56]. Ongoing preclinical investigations seeking to refine mesothelin-ADCs are underway[58,59].

*Mesothelin Chimeric Antigen Receptor (CAR) T Cells:* CAR-T cells are engineered to identify cancer-specific cell surface antigens and promote cell lysis via activation of an intracellular domain of the T cell receptor-CD3 complex and, in some cases, additional intracellular co-stimulatory molecules[60]. CAR-T cell products are now available for patients with several different types of refractory hematologic malignancies[61-64], and there is keen interest in exploring their applicability in solid tumors[65]. Given the overexpression of MSLN in DPM, anti-MSLN CAR-T cell constructs are in active development[65-68], with several approaches examining these agents either as single agents or in combination under investigation.

While CAR-T therapy can lead to a durable response in hematologic malignancies, several qualities of solid tumors have proven problematic, including heterogeneous antigen presentation, an inhospitable tumor microenvironment, and T-cell infiltration into a solid tumor[65,66,69]. In DPM, there have been multiple studies evaluating different MSLN-targeting CAR-T cell constructs and administration techniques (systemic *vs.* intrapleural; Table 3). Evaluations to date have mostly been in phase I clinical trials focused on safety and

**Table 2. Mesothelin-ADCs in mesothelioma**

| NCT ID | Phase | Product | Target patient population | Outcomes | Reference |
|---|---|---|---|---|---|
| NCT02610140 | 2 | Anetumab ravtansine | 248 patients with DPM randomized 2:1 to anetumab ravtansine versus vinorelbine | Anetumab ravtansine *vs.* vinorelbine: PFS: 4.3 *vs.* 4.5 months (HR 1.22, 95%CI: 0.85-1.74); OS: 11.6 *vs.* 9.5 months (HR 1.07, 95%CI 0.76-1.51) | [55] |
| NCT02341625 | 1/2a | BMS-986148 +/- nivolumab | 96 patients received BMS-986148 monotherapy ($n$ = 44 with DPM) and 30 received combination ($n$ = 16 with DPM) | Monotherapy: DCR: 56% ($n$ = 14) and ORR: 4% ($n$ = 1) in DPM patients Combination: DCR: 85% ($n$ = 11) and ORR: 23% ($n$ = 3) in DPM patients | [56] |

DPM: Diffuse pleural mesothelioma; PFS: progression-free survival; OS: overall survival; HR: hazards ratio; CI: confidence interval; DCR: disease control rate (stable disease + partial response).

tolerability, limiting our ability to speak to definitive efficacy. Furthermore, exploration of the combination of a CD28-costimulated mesothelin CAR-T with the iCaspase-9 safety gene and pembrolizumab has shown preliminary promise with a median OS of 23.9 months, 8 patients achieving stability for 6 months or more, and 2 patients with a complete response[75]. Larger prospective studies of novel CAR-T constructs and combinations are needed to better determine the safety, efficacy, and proper patient population to deploy this exciting treatment strategy.

***BRCA1-associated protein 1 (BAP1)***: BAP1 is a ubiquitin c-terminus hydrolase[14] which functions as a key tumor suppressor based on its role in both epigenetic modulation and DNA damage response[77]. Somatic and germline mutations in *BAP1* are associated with multiple solid malignancies, including a significant proportion of mesotheliomas[16,78-80], melanomas (uveal and cutaneous), clear cell renal cell carcinomas, and lung adenocarcinomas[14,81]. BAP1 inactivation increases the expression of enhancer of zeste homolog 2 (EZH2; also known as histone-lysine N-methyltransferase), which has itself been implicated as an oncogenic driver in DPMs[82]. Thus, BAP1 loss may sensitize such tumors to EZH2 inhibition. With nearly two-thirds of DPM tumors having inactivation of BAP1,[16,82] it is a key biomarker under clinical development [Table 4].

The EZH2 inhibitor tazemetostat is approved for later-line treatment of constitutively EZH2-activated tumors including epithelioid sarcomas with INI1/SMARCB1 loss[89] and follicular lymphomas harboring EZH2 mutations[90]. Given the enrichment of BAP1 inactivation in DPM, tazemetostat was explored in BAP1-inactivated DPM in a single-arm open-label phase 2 trial in 74 patients who were previously treated with platinum-based chemotherapy[83]. While the response rate was low (ORR 3% [$n$ = 2]), the disease control rate (DCR) was 54% at 12 weeks. This trial highlights a rationally designed targeted therapeutic approach for patients with DPM. Studies are ongoing to refine the population most likely to benefit from tazemetostat, as well as investigations into novel combinations.

Other efforts have focused on leveraging the role BAP1 plays in DNA repair and attempted to create conditions of synthetic lethality by employing poly ADP-ribose polymerase (PARP) inhibitors. PARP inhibitors have known efficacy across several solid tumors including approval in patients with ovarian[91,92] or breast cancers[93] harboring a germline *BRCA* mutation. The non-comparative multi-arm phase 2 Mesothelioma-Stratified Therapy 1 (MiST 1) trial was a novel clinical research platform study designed to stratify patients with DPM to targeted therapies after progression on first-line chemotherapy. Arm 1 of this trial enrolled 26 patients with cytoplasmic-BAP1-deficient or *BRCA1*-deficient mesotheliomas after platinum-based chemotherapy[85]. Patients received oral rucaparib twice daily for 24 weeks. DCR was 58% at 12 weeks and 23% at 24 weeks; partial responses were observed in three patients (12%). Furthermore, a similar single-arm phase II trial enrolled 23 patients with refractory mesothelioma to receive the PARP inhibitor olaparib[86]. Patients in this trial were *not* selected by *BAP1* alterations/loss (although 14 [61%]

**Table 3. Anti mesothelin CAR-T cell US clinical trials in mesothelioma**

| NCT ID | Phase | Product | Target patient population | Outcomes | Reference |
|---|---|---|---|---|---|
| **CAR-T +/- chemotherapy conditioning** | | | | | |
| NCT01355965 | 1 | Autologous mesothelin re-directed T cells | 18 patients with DPM. | 4 Patients treated with anaphylaxis, off-target toxicity | [70,71] |
| NCT02159716 | 1 | Lentiviral transduced CART-mesothelioma cells | 15 patients with DPM, ovarian ca, pancreatic ductal ca. | Cells well tolerated, expanded in blood, limited clinical activity | [72] |
| NCT03054298 | 1 | Lentiviral transduced fully human CART-mesothelioma cells | Up to 15 patients with mesothelin-expressing refractory DPM, lung cancer, and ovarian ca. | Study Ongoing | |
| NCT04577326 | 1 | M28z1XXPD1DNR: CAR T-cell with cell-intrinsic PD-1 blockade | 7 patients with DPM. | Study Ongoing | [73] |
| NCT01583686 | 1 | Anti-mesothelin CAR transduced peripheral blood lymphocytes + aldesleukin (IL-2) | 15 patients with mesothelin expressing metastatic disease. | Study Terminated for poor accrual | |
| NCT03608618 | 1 | MCY-M11: mesothelin targeting CAR-T- Intraperitoneal | 14 patients with ovarian Ca, primary peritoneal or fallopian tube ca, and peritoneal mesothelioma. | Following the treatment of 11 patients with initial feasibility and safety reported, study terminated-sponsor priority. | [74] |
| NCT05568680 | 1 | SynKIR-110:<br>T-cell transduced with mesothelin KIR-CAR | 42 patients with ovarian Ca, primary peritoneal Ca, ovarian or fallopian tube Ca, mesotheliomas, cholangiocarcinoma | Study Ongoing | |
| NCT05451849 | 1/2 | TC-510<br>T cell expressing both a mesothelin-CD3ε subunit and PD-1:CD28 switch receptor | 115 patients with advanced mesothelin-expressing tumors including DPM | Study Ongoing | |
| **CAR-T + Immune Checkpoint Inhibition** | | | | | |
| NCT02414269 | 1/2 | CD28-costimulated mesothelin CAR with the Icaspase-9 safety gene (*IcasM28z*) + pembrolizumab (mesothelioma cohort only) | 113 patients with mesothelin expressing malignant pleural disease. | 19 DPM patients: 2 complete metabolic response on PET, 5 partial response, 4 stable disease.<br>Study Ongoing. | [75] |
| NCT03907852 | 1/2 | Gavocabtagene autoleucel (autologous anti-mesothelin TCR fusion construct [TRuC]) with and without nivolumab or ipilimumab/nivolumab | 175 patients with advanced mesothelin-expressing cancers | Tumor regression in first 5 patients treated.<br>Study ongoing. | [76] |

CA: Cancer; CAR: chimeric antigen receptor; DPM: diffuse pleural mesothelioma.

patients in the trial had *BAP1* alterations). In this unselected population, olaparib had limited activity, with one (4%) partial response. In this small sample, germline *BAP1* mutations were associated with decreased OS compared to wild type (4.6 *vs.* 9.6 months, respectively, $P = 0.004$).

Base excision repair (BER) is a coordinated cellular process by which damaged DNA base pairs can be excised and repaired[94]; inhibition of this pathway in a tumor with DNA damage repair deficiencies, such as BAP1 loss, could lead to synthetic lethality. A recent phase 1 trial examined the safety and activity of TCR102, a BER pathway inhibitor, in combination with chemotherapy for the treatment of multiple advanced solid tumors[87]. In the DPM cohort, 14 patients

**Table 4. BAP1 targeted therapy in mesothelioma**

| NCT ID | Phase | Product | Target patient population | Outcomes | Reference |
|---|---|---|---|---|---|
| NCT02860286 | 2 | Tazemetostat; EZH2 inhibitor | 74 patients with previously treated BAP1 inactivated DPM | PFS: 18 weeks; OS: 36 weeks; ORR 3%; DCR: 54% at 12 weeks | [83] |
| NCT04104776 | 1/2 | CPI-0209; EZH2 inhibitor | 213 patients with advanced solid tumors and lymphomas including a cohort for BAP1 loss mesotheliomas | Study Ongoing | [84] |
| NCT03654833 | 2 | Rucaparib; PARP inhibitor | 26 patients with previously treated BAP1-deficient or BRCA1-deficient mesotheliomas | DCR at 12 weeks: 58%; manageable toxicity | [85] |
| NCT03531840 | 2 | Olaparib; PARP inhibitor | 23 patients with previously treated mesotheliomas, regardless of BAP1 status | All comers: PFS: 3.6 months and OS: 8.7 months<br>Germline *BAP1* mutation ($n$ = 4) *vs.* wildtype: PFS: 2.3 *vs.* 4.1 months ($P$ = 0.02); OS: 4.6 *vs.* 9.6 months ($P$ = 0.004) | [86] |
| NCT05455424 | 2 | Niraparib; PARP inhibitor | 84 patients with previously treated DPM randomized to niraparib *vs.* active symptom control | Study Ongoing | |
| NCT04515836 | 2 | Olaparib; PARP inhibitor | 56 patients with previously treated DPM harboring mutations in homologous recombination repair | Study Ongoing | |
| NCT02535312 | 1/2 | Pemetrexed + TCR102; BER pathway inhibitor | 16 patients with previously treated DPM | PFS: 4.3 months; 2 patients with partial responses | [87] |
| NCT04940637 | 2 | niraparib + dostarlimab | 70 patients with PD-L1 +, HRd + MPM or NSCLC | Study Ongoing | [88] |

DPM: Diffuse pleural mesothelioma; PFS: progression-free survival; OS: overall survival; DCR: disease control rate (stable disease + partial response); ORR: overall response rate.

were treated with TCR102 in combination with pemetrexed resulting in two (14%) partial responses and acceptable toxicity at the RP2D, meeting the prespecified criteria to warrant further exploration. A phase 2 continuation of this trial is ongoing (NCT02535312).

***Wilms Tumor 1 Protein* (WT1):** WT1 is a human self-antigen presented on the surface of cells, which plays a role in regulating cell proliferation and tumorigenesis. WT1 is limited to low-level expression in normal adult tissues, but the expression is enriched in several tumors, including 72%-93% of DPM[9,10,95-98], making it a provocative target for therapeutic exploitation.

A randomized phase 2 trial sought to evaluate the efficacy of a WT1 targeting peptide vaccine, Galinpepimut-S, in the adjuvant treatment of DPM. The study randomized 41 patients who had completed multimodality therapy for resectable DPM to either standard-of-care adjuvant chemotherapy and granulocyte-macrophage colony-stimulating factor (GM-CSF) with or without Galinpepimut-S. The study found the vaccine to be tolerable and a signal of improved OS (22.8 *vs.* 18.3 months) and PFS (10.1 *vs.* 7.4 months) compared to standard adjuvant chemotherapy alone; however, due to the control arm closing early for futility and the trial not being designed for a direct comparison of the two arms, a definitive efficacy signal could not be ascertained[99]. Further exploration of the WT1 vaccine is underway in a phase 1 study investigating the potential synergistic effects of Galinpepimut-S in combination with the anti-PD-L1 agent nivolumab for the treatment of patients with relapsed/refractory DPM (NCT04040231).

***NF2/YAP/TAZ:*** Genetic alterations in neurofibromatosis type 2 (*NF2*) are found in approximately 40% of DPM specimens[100-102].The *NF2* gene encodes moesin-ezrin-radixin-like (Merlin) tumor suppressor, and its inactivation is associated with the loss of Merlin protein expression in mesothelioma cells[103-105]. Merlin

regulates the HIPPO pathway by negatively regulating transcriptional co-activators YAP and TAZ through the E3 ubiquitin ligase $CRL4^{DCAF1}$; YAP and TAZ disinhibition results in an oncogenic cascade predisposing to the development of DPM[106-109]. Due to the genomic enrichment of *NF2* alterations in DPM (19%-25%)[8,22], several trials evaluating this pathway in patients with *NF2*-altered DPM have been conducted or are underway [Table 5].

The oral small-molecule focal adhesion kinase (FAK) TKI defactinib has been investigated in multiple solid tumor types, including ovarian, colorectal, pancreatic, and lung cancers[112]. Defactinib selectively kills Merlin-expressing cells through a FAK-Merlin synthetic lethal pathway. In a large, global, randomized phase II trial, 344 patients with DPM and with disease control after 4 cycles of first-line platinum/pemetrexed-based chemotherapy were assigned to receive either defactinib or placebo; Unfortunately, neither PFS nor OS was improved with defactinib[110]. Trials evaluating other inhibitors of this pathway are underway, including (1) Nedd8-activating enzyme (NAE) inhibitors which result in decreased formation of $CRL4^{DCAF1}$(NCT03319537); and (2) YAP/TEAD inhibitors (NCT04857372).

***CDKN2, p16, MTAP:*** Co-deletion of the *CDKN2A* and *methylthioadenosine phosphorylase (MTAP)* genes is notably enriched in 28%-49% of DPM[8,16,22,113,114]. The proximity of the *CDKN2A* gene on chromosome 9p21 to *MTAP* predisposes the loss of both genes with the loss of one allele[115,116]. *CDKN2A* encodes p16INK4a and p14AR, important cell cycle modulators which regulate cyclin-dependent kinases (CDKs)[117-119]. Enrichment of these alterations poses distinct mechanistic vulnerabilities under investigation: (1) *P*rotein arginine methyltransferase 5 (PRMT5); and (2) Cyclin-dependent kinase (CDK) inhibition [Table 6].

*In vitro*, PRMT5 inhibition has been evaluated as a potential therapy against *MTAP*-deficient cancers, including DPM[121]. Early phase clinical trials of the safety and possible roles of PRMT5 inhibitors in solid tumors, including DPM, are currently underway (NCT05245500, NCT05275478, NCT04794699). Direct CDK4/6 inhibitors have synthetic lethality in DPM[122,123] and are under active investigation. In the single-arm, phase 2, MiST 2 trial, 26 patients with p16INK4A-deficient DPM whose disease had progressed after platinum-based chemotherapy received the oral CDK4/6 inhibitor, abemaciclib. The study met its primary endpoint, with a DCR of 54% at 12 weeks, tumor volume reductions in 80% of evaluable patients, and four patients who achieved a partial response[120]. These results are encouraging evidence of possible antitumor effects, but a larger randomized trial and further refinement of possible biomarkers are needed to determine any possible place in our current clinical practice[124,125].

**V-domain Ig suppressor T cell activation (VISTA):** VISTA is a negative immune checkpoint regulator of myeloid and T cell function with high levels of expression in DPM (85%)[17]. *In vivo* studies suggest anti-VISTA antibodies have promising antitumor activity[16,17,126]. With the integration of 1L immunotherapy into the treatment paradigms for DPM[18], exploration of later-line treatment options to improve response and/or rechallenge to immunotherapy is needed. A phase 1 study of CA-170 (small molecule inhibitor of PD-L1 and VISTA)[127] in patients with previously treated advanced solid tumors and lymphomas exhibited an acceptable toxicity profile[128] and is currently under development. The VISTA inhibitor CI-8993 is currently under investigation in a phase I study evaluating the safety and activity of this antibody in patients with previously treated advanced solid tumors (NCT04475523).

**Argininosuccinate synthetase 1 (ASS1):** ASS1 is a key enzyme in the urea cycle required for the formation of arginine, and ASS1-deficiency has been implicated in tumorigenesis by supporting cellular proliferation and pyrimidine synthesis[129,130]. Certain solid tumors, including nearly two-thirds of DPM, have inherent enrichment for ASS1-deficiency[131] and mechanistically lend themselves to therapeutic exploitation with

**Table 5. NF2/YAP/TAZ targeted therapy in mesothelioma**

| NCT ID | Phase | Product | Target patient population | Outcomes | Reference |
|---|---|---|---|---|---|
| NCT01870609 | 2 | Platinum pemetrexed +/- defactinib maintenance; FAK inhibitor | 344 patients with previously treated DPM randomized 1:1 after 4 cycles of chemotherapy to defactinib maintenance or placebo | Maintenance *vs.* placebo: PFS: 4.1 *vs.* 4.0 months; OS: 12.7 *vs.* 13.6 months (HR 1.0, 95%CI: 0.7-1.4) | [110] |
| NCT00770120 | 2 | Everolimus; mTOR inhibitor | 59 patients with DPM treated with ≤ 1 prior chemotherapy regimen | ORR: 0%; PFS 2.9 months; OS 6.3 months | [111] |
| NCT01024946 | 2 | Everolimus; mTOR inhibitor | 39 patients with previously treated DPM with NF2 loss | Closed early, given tolerability after enrolling 11 patients (6 evaluable) | |
| NCT05228015 | 1 | IK-930; TEAD inhibitor | 158 patients with previously treated advanced solid tumors | Study ongoing | |
| NCT04857372 | 1 | IAG933; YAP/TEAD inhibitor | 156 patients with previously treated DPM and other solid tumors | Study ongoing | |
| NCT04665206 | 1 | VT3989; TEAD inhibitor | 80 patients with refractory solid tumors, including DPM with NF2 loss | Study ongoing | |
| NCT03319537 | 1/2 | Pevonedistat; NEDD8 inhibitor | Monotherapy: Previously treated patients with NF2 altered DPM; Pevonedistat + platinum/pemetrexed: Treatment naïve patients with DPM | Closed to accrual | |

DPM: Diffuse pleural mesothelioma; PFS: progression-free survival; OS: overall survival; ORR: overall response rate; HR: hazard ratio; CI: confidence interval.

**Table 6. CDKN2/p16/MTAP targeted therapy in mesothelioma**

| NCT ID | Phase | Product | Target Patient Population | Outcomes | Reference |
|---|---|---|---|---|---|
| NCT03654833 | 2 | Abemaciclib; CDK4/6 inhibitor | 27 eligible patients with previously treated DPM with IHC noting p16ink4A deficiency | DCR at 12 weeks: 54%; PFS: 128 days; OS: 217 days | [120] |
| NCT05538572 | 1 | PRT3645; CDK4/6 inhibitor | 51 patients with previously treated advanced solid tumors | Study ongoing | |
| NCT05245500 | 1/2 | MRTX1719; PRMT5-MTA inhibitor | 339 patients with previously treated advanced MTAP-deleted solid tumors | Study ongoing | |
| NCT05275478 | 1 | TNG908; PRMT5 inhibitor | 170 patients with previously treated MTAP-deleted solid tumors | Study ongoing | |
| NCT04794699 | 1 | IDE397; MAT2A Inhibitor | 382 patients with previously treated MTAP-deleted advanced solid tumors | Study ongoing | |

DPM: Diffuse pleural mesothelioma; PFS: progression-free survival; OS: overall survival; DCR: disease control rate (stable disease + partial response); IHC: immunohistochemistry.

arginine deprivation therapy by pegylated arginine deaminase (ADI-PEG 20). The phase 2 study of ADI-PEG 20 in combination with cisplatin/pemetrexed in 32 patients with previously untreated ASS1-deficient DPM showed promising clinical benefit (DCR: 93.5%, PFS: 5.6 months, OS: 10.1 months)[132]. The trial expanded into the randomized phase 3 ATOMIC-MESO trial (NCT02709512) comparing cisplatin/pemetrexed with or without ADI-PEG 20 with a recent press release indicating it has met the prespecified endpoint with a median OS of 9.3 *vs.* 7.7 months (HR: 0.71; 95%CI: 0.55-0.93) and PFS of 6.1 *vs.* 5.6 months (HR: 0.65; 95%CI: 0.47-0.90); there is a current plan to submit for regulatory consideration[133]. This landmark positive trial marks a major step forward in our efforts to integrate targeted agents into the treatment of DPM.

## CONCLUSION

With a growing understanding of the molecular underpinnings of DPM, there has been a multitude of rationally designed clinical trials looking to exploit potential therapeutic vulnerabilities. Newer generations of agents, including CAR-T therapies targeting mesothelin and arginine-deprivation therapies for ASS1 deficient mesotheliomas, hold particular promise, and aim to overcome the historically poor response rates in targeted therapies for mesothelioma.

The preponderance of disappointing trial results described here, however, highlights the struggle to translate promising preclinical data into patient care. To propel the field forward, we must continue to collaborate to establish preclinical models that faithfully recapitulate DPM biology for *in vivo* testing[134] and strive to better refine biomarkers and patient selection criteria for trials of targeted therapy in DPM. Investigation of several promising preclinical targets (e.g., microRNAs) is underway but has not yet been translated into clinical investigation[135]; Future trials need to incorporate comprehensive pathologic, genomic, and expression level data of enrolled patients to better understand those who benefit from a treatment and refine future trial designs[136]. To accomplish this will require building platforms for close iterative collaboration between medical and surgical oncologists, pathologists, and laboratory-based genomic and pharmacologic scientists; this investment is critical to improving therapeutic options for patients with DPM.

## DECLARATIONS

### Authors' contributions

The following authors made substantial contributions to the conception and design of the work, literature review, technical support, and writing of the work: Offin M, Fitzgerald B, Zauderer MG, Doroshow D

### Availability of data and materials

Not applicable.

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### Conflicts of interest

Michael Offin has consulted with Novartis, Jazz, and PharmaMar regarding oncology drug development. Michael Offin has received an honorarium from Targeted Oncology, OncLive, and the American Society for Radiation Oncology.

Bailey Fitzgerald has no relevant conflicts to declare.

Marjorie G. Zauderer has received consulting fees from Ikena, Takeda, GlaxoSmithKline, Aldeyra Therapeutics, and Novocure and honoraria for CME content from PER, Medscape, Research to Practice, Medical Learning Institute and OncLive. Memorial Sloan Kettering receives research funding from the Department of Defense, the National Institutes of Health, Precog, GlaxoSmithKline, Epizyme, Polaris, Sellas Life Sciences, Bristol Myers Squibb, Millenium/Takeda, Curis, and Atara for research conducted by Marjorie G. Zauderer. Marjorie G. Zauderer serves as Chair of the Board of Directors of the Mesothelioma Applied Research Foundation, an uncompensated position.

Deborah Doroshow has received consulting fees from AstraZeneca and Mirati Therapeutics and honoraria from PER, OncLive, and Targeted Oncology.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.



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