REVIEW ARTICLE

BAP1-loss in mesothelioma: molecular mechanisms and clinical opportunities

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Mesothelioma is an aggressive cancer that is often characterized by loss of the *BRCA1-associated protein 1* (*BAP1*) tumor suppressor gene. This alteration typically occurs as an early clonal event in mesothelioma development, making it a promising candidate for both diagnostic and therapeutic applications. Functionally, BAP1 regulates gene expression through interactions with Polycomb-group complexes, and it plays roles in various other cellular processes including DNA repair, replication stress, and cell metabolism. While preclinical research has identified multiple potential vulnerabilities in *BAP1*-deficient tumors—including sensitivity to EZH2-, HDAC-, PARP-, and FGFR-inhibitors—translating these findings to the clinic remains a challenge. In this review, we provide a comprehensive overview of BAP1's molecular functions in mesothelioma, with a focus on their translation into clinical therapeutics for this hard-to-treat malignancy.

Oncogene (2026) 45:593–602; https://doi.org/10.1038/s41388-025-03672-x

INTRODUCTION

Mesothelioma is a rare and aggressive cancer of the pleural lining of the lungs, strongly associated with the inhalation of asbestos fibers. The disease was initially observed in asbestos workers in the late 19th and early 20th centuries [1], and the causal link between asbestos and mesothelioma was later confirmed in several landmark epidemiological studies [2, 3]. These findings led to a ban on the production and sale of asbestos-containing materials in most developed countries by the early 1990s, although these materials remain in use in many countries across the world. Moreover, due to a long latency period between asbestos exposure and disease onset [4] and the continued presence of asbestos in many older buildings, mesothelioma remains a significant clinical challenge.

At the molecular level, mesothelioma is characterized by frequent loss of tumor suppressors [5, 6]. Alterations in the *BRCA1-associated protein 1* (*BAP1*) tumor suppressor gene are some of the most common alterations in mesothelioma, and may occur either somatically in sporadic mesothelioma cases [7], or through germline alterations in the hereditary *BAP1* tumor predisposition syndrome (*BAP1*-TPDS) [8–11]. Patients with this syndrome often develop mesothelioma without asbestos exposure and have an elevated risk of other *BAP1*-associated malignancies, including renal cell carcinoma, melanocytic tumors, basal cell carcinoma, and metastatic uveal melanoma [9, 10], which they often develop at a younger age than in *BAP1*-wildtype individuals [10, 12, 13].

Mechanistically, BAP1 interacts with Polycomb-group proteins and regulates gene expression through de-ubiquitination of histone H2A [14–18]. BAP1 has also been implicated in a range of other cellular functions including DNA repair, replication stress, and cell metabolism. Although no therapies currently exist to restore BAP1's tumor suppressor function, preclinical studies into its molecular functions have revealed multiple promising therapeutic vulnerabilities. These include synthetic lethality strategies that target specific vulnerabilities in *BAP1*-deficient cells, and emerging links between *BAP1*-loss, the immune microenvironment, and immunotherapy response. Moreover, *BAP1*-deficiency has been explored as a predictive and prognostic biomarker for treatment response, and was shown to be an effective biomarker for the diagnosis of mesothelioma.

In this narrative review, we summarize recent insights into the molecular function of BAP1 in mesothelioma, evaluate its value as a biomarker, and explore opportunities for therapeutic strategies. We highlight findings from preclinical studies, mouse models, and clinical trials, and discuss novel translational avenues for BAP1-directed strategies in both the somatic and germline BAP1-loss cases.

SCOPE AND METHODS

For this narrative review, we evaluated peer-reviewed, full-text articles published in English up to June 2025. A core PubMed search query using the terms: '*(BAP1 [tiab] AND mesothelioma [tiab]) OR (BAP1 [tiab] AND clinical trial [pt]) NOT review [pt]*' was used, yielding 443 PubMed abstracts that were screened for inclusion using Rayyan software [19]. We also screened reference lists of relevant papers, and performed targeted searches for additional studies related to BAP1 biology and its clinical implications in mesothelioma.

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Received: 12 September 2025 Revised: 25 November 2025 Accepted: 15 December 2025
Published online: 7 January 2026

Table 1. Frequency of BAP1 alterations in mesothelioma.

Study	Histological subtype	Sample size	Frequency of BAP1 alterations
Bott et al. [7]	Pleural	53	23% (mutations only)
Nasu et al. [20]	Pleural and peritoneal	92	66% (mutations + CNVs)
Alakus et al. [21]	Peritoneal	12	66% (mutations + CNVs)
Leblay et al. [22]	Peritoneal	46	73% (mutations + CNVs)

Table 2. BAP1 immunohistochemistry in mesothelioma diagnosis.

Study	Sample type	Sample size (meso/benign)	BAP1 loss (meso/benign)	Specificity (%)	Sensitivity (%)
Cigognetti et al. [31]	Biopsy + Cytology	254 (212/42)	66%/0%	100	66.0
Yoshimura et al. [32]	Biopsy	67 (38/29)	52.6%/0%	100	52.6
Cozzi et al. [33]	Biopsy + Cytology	165 (121/44)	68.8%/0%	100	76.5
Andrici et al. [34]	Cytology	232 (75/157)	57%/5%	95	57.0

BAP1-loss is an early and frequent event in mesothelioma development

The genomic landscape of mesothelioma is characterized by frequent inactivation of tumor suppressors including *BAP1*, *CDKN2A*, *NF2*, and *LATS1/2* [5, 6]. Among these, *BAP1* is one of the most commonly altered genes, with *BAP1*-loss occurring in ~66–73% of all sporadic pleural mesothelioma cases [7, 20–22] (Table 1), and in all individuals with *BAP1* tumor predisposition syndrome (*BAP1*-TPDS) [9–11]. Phylogenetic analysis of human mesothelioma samples has shown that *BAP1*-loss typically occurs as an early truncal (clonal) event that is detectable in nearly all tumor cells [23]. This clonal uniformity enhances *BAP1*'s appeal as a therapeutic target, as strategies that exploit *BAP1*-deficiency may affect the majority of the malignant cell population.

The tumor-suppressive function of BAP1 was first demonstrated in vitro, where it was shown to interact with BRCA1, a key regulator of DNA repair and cell cycle control [24]. Subsequent in vivo studies in genetically engineered mouse models confirmed BAP1's causative role in mesothelioma development, as deletion of *Bap1* in mice induces rapid formation of highly aggressive pleural tumors [25, 26]. Underscoring BAP1's protective role against both spontaneous and asbestos-induced mesothelioma, studies in germline BAP1-loss patients have shown enhanced sensitivity to asbestos-induced mesothelioma [27], which has also been observed in *Bap1*-deficient mice models [28]. This interaction between asbestos exposure and *BAP1*-loss might be explained by BAP1's role in ferroptosis regulation, which may provide a selective advantage for *BAP1*-deficient cells in the reactive oxygen-rich environment of asbestos-exposed tissues [29].

BAP1-loss as a diagnostic and prognostic marker in mesothelioma

Loss of nuclear *BAP1* expression, as detected by immunohistochemistry (IHC), has become an important diagnostic tool for distinguishing mesothelioma from benign mesothelial proliferations [30]. *BAP1* IHC can be performed on both tumor biopsies and cytology samples, and shows high specificity (95–100%) and moderate sensitivity (52.6–76.5%) for detecting mesothelioma [31–34] (Table 2). Its diagnostic sensitivity can be improved by combining *BAP1* staining with additional markers such as *p16* (*CDKN2A*) and *MTAP* cytoplasmic loss of expression, which are also frequently altered in mesothelioma [30]. Loss of *BAP1* is more frequently associated with the epithelioid/biphasic subtype compared to the non-epithelioid subtype [31, 33].

Two recent studies have reported moderate predictive performance for non-invasive detection of *BAP1*-status by radiomics-based analysis of CT scans [35, 36], although sample sizes were relatively small ($n = 74$; $n = 149$) and the specificity of this approach remains lower than that of IHC-based methods (AUC ~ 0.69–0.77). Moreover, the external generalizability of these models has yet to be established.

In terms of prognosis, germline *BAP1*-loss has been associated with slower tumor progression and longer overall survival compared to *BAP1*-proficient mesothelioma [10, 37, 38] (Table 3), possibly due to slower tumor cell proliferation and/or metabolic changes [39]. Moreover, *BAP1* status might affect tumor inflammation in mesothelioma (as discussed below), which could also affect tumor progression. For somatic *BAP1* alterations, the prognostic value is less clear with some studies reporting a modest survival benefit (typically 4–10 months improvement in median overall survival), while others fail to find a significant association [40–43] (Table 3).

Germline BAP1-related mesotheliomas show distinct biological and clinical characteristics

The biological and clinical features of germline *BAP1*-related mesotheliomas were recently characterized in detail by Carbone et al. [10], in an investigation of 361 individuals from 47 families carrying *BAP1* alterations (238 $BAP1^{+/-}$; 123 $BAP1^{+/+}$). All germline BAP1-related mesotheliomas in this cohort were of epithelioid histology, showing tubulopapillary and/or trabecular architecture, with no sarcomatoid tumors reported. Notably, none of the $BAP1^{+/+}$ siblings developed mesothelioma, and—with one exception—none of the affected individuals had any known history of asbestos exposure.

Thoracoscopic evaluation revealed multiple synchronous pleural and peritoneal lesions, presenting as flat whitish areas or millimeter-sized nodules. In these lesions, mesothelial cells were found within or replacing the sub-mesothelial fat layer and were enclosed in dense, collagen-rich reactive stroma that was often associated with inflammatory cell infiltrates. These lesions were termed 'low-grade germline-mutant-BAP1-associated mesotheliomas' (L-BAMs). Unlike sporadic *BAP1*-deficient lesions, L-BAMs may remain indolent and are sometimes misdiagnosed as tricavitary stage IV metastatic mesothelioma, even though many patients experience prolonged survival.

Cancer-screening programs may be crucial for early detection of progression in these families, and should include surveillance for other *BAP1*-related cancers, notably uveal melanoma and renal cell carcinoma. Given their less aggressive clinical behavior, extensive interventions such as surgery or systemic treatments may not be immediately required, as lesions can remain stable for years.

These findings also underscore the need for (pre-)clinical studies to explicitly report the germline or somatic status of

Table 3. Prognostic significance of BAP1 mutations in mesothelioma.

Study	Histological subtype	Germline or somatic?	Sample size (altered/wildtype)	Median OS (altered vs. wildtype)	Statistical significance	Prognostic implication of BAP1 loss
Baumann et al. [37]	Pleural and peritoneal	Germline	23 (23/0)	60.0 months vs. 9 months	–	Better prognosis (germline BAP1 carriers vs. SEER cohort)
Pastorino et al. [38]	Pleural and peritoneal	Germline	79 (43/36)	60.0 months vs. 8 months	–	Better prognosis (germline BAP1 carriers vs. SEER cohort)
Zauderer et al. [40]	Pleural	Somatic	121 (24/97)	14.3 months vs. 14.8 months	$p = 0.81$	Not associated with prognosis
McGregor et al. [41]	Pleural	Not specified	88 (51/37)	13.0 months vs. 9.2 months	$p < 0.05$	Better prognosis (significant)
Singhi et al. [42]	Peritoneal	Not specified	86 (49/37)	–	$p = 0.780$	Not associated with prognosis
Farzin et al. [43]	Not specified	Not specified	229 (106/123)	16.1 months vs. 6.3 months	$p < 0.01$	Better prognosis (significant)

BAP1-alterations, as this may significantly influence their biological and clinical behavior and prognosis.

BAP1 in transcriptional and chromatin regulation

Transcriptional regulation by BAP1 through Polycomb complexes. The canonical molecular function of BAP1 involves the regulation of gene expression through its interactions with Polycomb group (PcG) chromatin-modifying complexes (Fig. 1a). PcG complexes were first identified in *Drosophila* as key regulators of Hox gene expression during early embryonic development [44]. In mammals, these roles are conserved and include the control of embryonic patterning, X-chromosome inactivation, and maintenance of embryonic stem cells (as reviewed by refs. [45, 46]). Beyond their role in development, PcG proteins also contribute to cancer development [47], most notably through the silencing of tumor suppressor gene CDKN2A [48], which is also frequently inactivated in mesothelioma.

The two major PcG complexes, Polycomb Repressive Complex 1 (PRC1) and Polycomb Repressive Complex 2 (PRC2) repress gene expression by depositing the histone marks H2AK119ub and H3K27me3, respectively (as reviewed in refs. [45, 46]). These repressive marks are dynamically regulated and are counterbalanced by the Polycomb Repressive Deubiquitinase (PR-DUB) complex. BAP1 is the core catalytic component of PR-DUB and specifically removes the ubiquitin group from mono-ubiquitinated H2AK119 [14–18]. Through this activity, BAP1 plays a central role in modulating chromatin accessibility and regulating gene expression programs.

BAP1-loss and sensitivity to EZH2 inhibitors. The gene regulatory function of BAP1 has potential therapeutic implications in mesothelioma. Preclinical studies have shown that *BAP1*-loss leads to enhanced activity of PRC2 and increased deposition of the repressive histone mark H3K27me3 [49]. As a result, *BAP1*-deficient cells become dependent on the catalytic function of EZH2, which is the methyltransferase subunit of PRC2. This dependency might be therapeutically targeted using EZH2 inhibitors (Fig. 1a), and both in vitro and in vivo studies have demonstrated that the small-molecule inhibitor EPZ011989 selectively suppressed *BAP1*-deficient mesothelioma cell and tumor growth in mice [49].

These findings led to the proposal that EZH2 inhibitors could be a targeted therapy for *BAP1*-deficient mesothelioma. However, early clinical trial results have shown limited results. In a phase II trial for the EZH2 inhibitor tazemetostat in 73 patients with *BAP1*-deficient pleural mesothelioma, the 12-week disease control rate was 54%, with only two patients (2.7%) achieving a partial response and none achieving complete responses [50]. Future studies may investigate whether newly developed next-generation EZH2 inhibitors can improve potency and/or selectivity [51]. In addition, alternative biomarkers such as *CDKN2A* may help to stratify patients for EZH2 inhibitor treatment [52]. Moreover, combination therapies that enhance the efficacy of EZH2 inhibitors in *BAP1*-deficient tumors are currently under investigation [53–55], and will be discussed below.

BAP1-loss and sensitivity to HDAC inhibitors. In addition to its canonical role in Polycomb-mediated transcriptional regulation, BAP1 has also been shown to interact with histone deacetylase proteins such as HDAC1. A study investigating the molecular mechanisms underlying mesothelioma susceptibility in patients with *BAP1*-TPDS found that BAP1 forms a trimeric complex with HMGB1 and HDAC1 [56] (Fig. 1b). This interaction leads to deubiquitination and stabilization of HDAC1, resulting in deacetylation and nuclear retention of HMGB1. HMGB1 functions as a nuclear protein involved in transcriptional regulation, but may also be released upon chronic inflammation, such as after asbestos exposure, and has been implicated in mesothelioma development [57]. In $Bap1^{+/-}$ mice, inhibition of HMGB1 decreased the

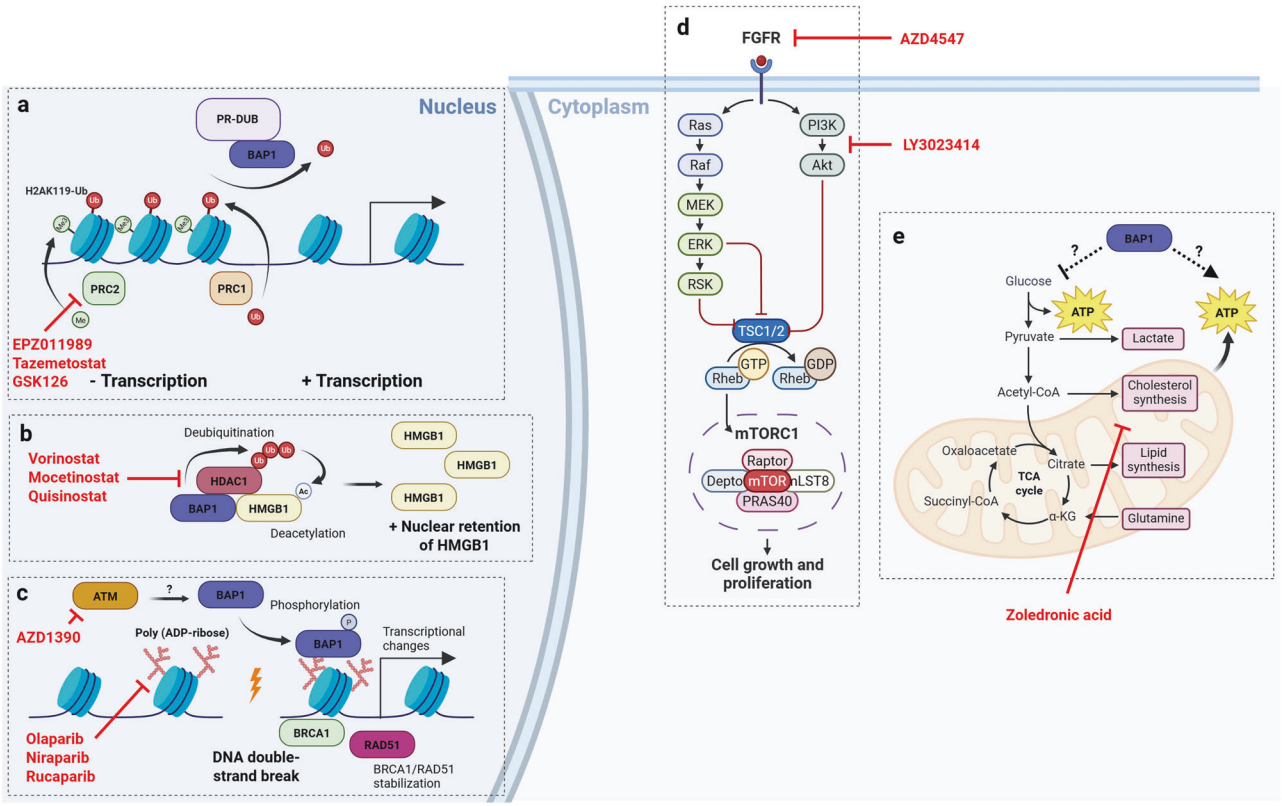

Fig. 1 Molecular mechanisms and therapeutic opportunities for BAP1-deficient mesothelioma. a BAP1 regulates transcription as part of the PR-DUB complex, removing H2AK119ub deposited by PRC1 and counteracting PRC2-mediated repression. Loss of BAP1 shifts chromatin balance toward repression, creating dependency on PRC2 and sensitivity to EZH2 inhibitors (EPZ011989, tazemetostat, GSK126). **b** BAP1 forms a trimeric complex with HDAC1 and HMGB1, stabilizing HDAC1 and promoting HMGB1 deacetylation and nuclear retention. HDAC inhibitors (vorinostat, mocetinostat, quisinostat) may disrupt this interaction and show increased activity in BAP1-deficient cells. **c** BAP1 contributes to DNA double-strand break repair by stabilizing BRCA1 and RAD51. BAP1-loss sensitizes cells to PARP inhibitors (olaparib, niraparib, rucaparib) in vitro, though clinical translation remains limited. ATM inhibitors (AZD1390) have also shown synthetic lethality in preclinical studies. **d** BAP1-deficient mesotheliomas display sensitivity to FGFR inhibition (AZD4547) and possibly PI3K–mTOR inhibition (LY3023414), although the mechanistic link between BAP1-loss and these pathways is not fully defined. **e** BAP1-loss has been linked to metabolic reprogramming, including increased glycolysis and altered lipid and cholesterol metabolism. Drug screens have identified the mevalonate/cholesterol synthesis pathway as a potential vulnerability, with zoledronic acid showing efficacy in BAP1-deficient preclinical models.

incidence of mesothelioma following asbestos exposure, suggesting that this trimeric interaction may provide a strategic therapeutic target for reducing mesothelioma incidence in *BAP1*-TPDS patients [56].

This hypothesis was supported by preclinical studies showing that *BAP1*-deficient mesothelioma and uveal melanoma are more sensitive to HDAC inhibitors, including vorinostat, mocetinostat, and quisinostat [58–60] (Fig. 1b). However, the phase III VANTAGE-014 trial, which tested the HDAC inhibitor vorinostat as second- or third-line therapy in patients with advanced pleural mesothelioma, did not show improvement in progression-free or overall survival compared to placebo [61]. This study did not stratify patients based on *BAP1* status, and did not assess its interaction with treatment response. Future retrospective analyses or biomarker-enriched trials could definitively clarify whether *BAP1*-loss or *HMGB1*-related biomarkers can predict HDAC inhibitor sensitivity more accurately.

Clinically explored synthetic lethalities for *BAP1*-deficient mesotheliomas

Synthetic lethality as a therapeutic strategy. While there are currently no approved or investigational therapies that restore BAP1 function, an alternative strategy is to exploit synthetic lethal interaction in *BAP1*-deficient tumors [62]. These are genetic dependencies that arise when the loss of one gene (e.g., *BAP1*) sensitizes the cells to inhibition of a second, non-essential gene. This concept has already led to new therapeutic options for some tumors with specific tumor suppressor deficiencies.

The paradigmatic example of a synthetic lethal interaction is the use of poly(ADP-ribose) polymerase (PARP) inhibitors to treat *BRCA1*-deficient breast and ovarian cancers. *BRCA1*, a frequently inactivated tumor suppressor in these cancers, plays a central role in DNA damage repair via the homologous recombination (HR) pathway [63, 64]. Tumors that lack functional BRCA1 are highly sensitive to PARP-inhibitors such as olaparib, which block an alternative DNA repair pathway and thereby selectively kill *BRCA1*-deficient cells [65, 66]. Exploiting such selective vulnerabilities through synthetic lethality opens up new approaches to target mutations that are otherwise considered undruggable.

BAP1-loss and sensitivity to PARP inhibitors. BAP1 was originally identified as a BRCA1-interacting protein [24], raising the possibility that *BAP1*-deficient mesothelioma cells might also be selectively sensitive to PARP inhibitors. Like BRCA1, BAP1 is involved in the maintenance of genome integrity through multiple mechanisms (Fig. 1c). During DNA replication, BAP1 associates with the INO80 chromatin remodeling complex to facilitate the restart of stalled replication forks [67, 68]. Following DNA double-strand breaks, BAP1 is phosphorylated as serine 592, leading to transcriptional changes [69]. Knockout studies in cell lines have shown that BAP1 is recruited to sites of DNA damage and promotes the assembly of BRCA1 and RAD51 repair

complexes [70, 71], while also stabilizing BRCA1 protein levels [72], suggesting a role in homologous recombination repair. Moreover, BAP1 was also shown to interact with the alternative non-homologous end-joining (NHEJ) pathway of DNA double-strand break repair through interactions with DNA protein kinase (DNA-PK) [73]. Taken together, these preclinical results strongly suggest a key role for BAP1 in the DNA damage response in mesothelioma.

Based on these findings, PARP inhibitors were proposed as a targeted treatment for *BAP1*-deficient mesothelioma (Fig. 1c). However, while cell-line-based experiments demonstrated increased sensitivity of *BAP1*-deficient cells to PARP inhibitors [74, 75], these findings have not yet translated into clinical benefits for mesothelioma patients [76–79]. In the MiST1 phase II trial, which tested the PARP inhibitor rucaparib in *BAP1*- or *BRCA1*-deficient mesotheliomas, a 12-week disease control rate of 58% (95% CI: 37–77%) was observed [76]. However, *BAP1* status did not significantly correlate with objective response ($p = 0.22$). Similarly, the UNITO-001 phase II trial combined the PARP inhibitor niraparib with the anti-PD-1 agent dostarlimab in homologous recombination-deficient mesothelioma and non-small cell lung cancer (NSCLC), but found no meaningful clinical activity in mesothelioma patients with somatic *BAP1* alterations [77]. Notably, a smaller phase II trial testing olaparib in 23 previously treated mesothelioma patients actually reported a poorer progression-free and overall survival in *BAP1*-deficient ($n = 4$) compared to wild-type ($n = 19$) individuals [78].

Together, these results suggest that, despite a strong preclinical rationale, *BAP1* status alone may not reliably predict sensitivity to PARP inhibition in mesothelioma. Alternative avenues for optimizing PARP inhibitor treatment in mesothelioma are currently focused on biomarkers such as *SLFN11, CCDC6*, and *IFNα*, which have shown predictive value for PARP inhibitor treatment in mesothelioma [79–81].

BAP1-loss and sensitivity to FGFR inhibitors. Multiple fibroblast growth factor receptor (FGFR) inhibitors have been developed and approved for the treatment of various cancer types. A high-throughput compound screen in 899 cancer cell lines, including mesothelioma lines, identified a subset of mesothelioma cells with high sensitivity to FGFR inhibition [82]. Interestingly, while none of these sensitive lines harbored *FGFR* mutations, low *BAP1* expression was found to predict sensitivity to FGFR inhibitors. These findings were validated in two xenograft mouse models, supporting the therapeutic potential of the FGFR inhibitor AZD4547 in BAP1-deficient mesothelioma (Fig. 1d). A follow-up study confirmed the specificity of AZD4547 sensitivity to *BAP1*-deficient tumors and demonstrated that co-treatment with the EZH2 inhibitor GSK126 could further improve tumor volume reduction and survival [54].

The efficacy of oral AZD4547 was subsequently evaluated in a phase II clinical trial in patients with relapsed mesothelioma [83]. However, *BAP1* status was not used as an inclusion criterion, and the trial was eventually discontinued due to low progression-free survival at 6 months. A post-hoc analysis of *BAP1* expression by immunohistochemistry did not show any significant differences in outcomes between *BAP1*-low ($n = 19$; median PFS: 84 days; 95% CI: 62–139 days) and *BAP1*-high ($n = 5$; median PFS: 87 days; 95% CI: 58–134 days) mesotheliomas. The combination of AZD4547 with an EZH2 inhibitor has not yet been tested clinically, but may represent a promising avenue for future trials, especially in a biomarker-enriched population.

BAP1-loss and sensitivity to PI3K–mTOR inhibitors. The phosphoinositide 3-kinase–mechanistic target of rapamycin (PI3K–mTOR) pathway is one of the most commonly deregulated pathways across cancer types, and extensive efforts are ongoing to develop more effective PI3K–mTOR inhibitors for clinical use. The compound LY3023414 was recently evaluated in a phase I cohort expansion study in mesothelioma patients (Fig. 1d). While this study demonstrated that LY3023414 was safe and tolerable in these patients, it did not show significant anti-tumor activity [84]. A post-hoc analysis of tumor genomic alterations in these patients did not identify any genetic markers, including *BAP1* loss, that clearly correlated with treatment response. Nonetheless, given the rapid development of PI3K–mTOR inhibitor development and the complex roles of BAP1 in cellular metabolism and survival (see below), future studies may further explore whether *BAP1* status influences sensitivity to PI3K–mTOR inhibition.

Emerging preclinical strategies for *BAP1*-deficient mesothelioma

BAP1-loss may sensitize cells to ATM inhibitors. Although PARP inhibitors have shown limited clinical efficacy in mesothelioma, alternative DNA damage response pathways may also offer promising therapeutic vulnerabilities in *BAP1*-deficient tumors. One such target is the ataxia-telangiectasia mutated (ATM) serine/threonine kinase, which plays a central role in orchestrating the cellular response to DNA double-strand breaks (Fig. 1c). ATM inhibitors such as AZD1390 are currently in early-phase clinical trials, and were recently identified in a synergy drug screen as a promising combination partner for EZH2 inhibition in *BAP1*-deficient mesothelioma [53]. In vitro studies in human mesothelioma cell lines demonstrated that co-inhibition of ATM and EZH2 with a combination of AZD1390 and GSK126 selectively impaired *BAP1*-deficient, but not *BAP1*-proficient cell line growth [53]. This drug combination also produced a modest suppression of tumor growth in a *BAP1*-deficient xenograft mouse model, warranting further preclinical and clinical investigation.

In addition to PARP and ATM inhibitors, a broader class of DNA damage response inhibitors is currently under clinical trial evaluation and may hold potential in *BAP1*-deficient mesothelioma (as reviewed in ref. [85]). These compounds include inhibitors targeting pathways including ATR (ataxia telangiectasia and Rad3-related protein), MDM2/MDMX-p53 signaling, and PRMT5 (protein arginine methyltransferase 5), each of which may exploit distinct DNA repair vulnerabilities in *BAP1*-deficient mesotheliomas. A more systemic evaluation of these DNA damage response targeting agents in *BAP1*-deficient mesotheliomas is warranted.

BAP1-loss rewires cellular metabolism. While BAP1 is best known for its role in transcriptional regulation and the DNA damage response, recent studies have linked *BAP1*-loss to metabolic reprogramming in cancer (Fig. 1e). Metabolomic profiling of plasma from 61 individuals with germline *BAP1* alterations revealed a Warburg-like effect, characterized by increased aerobic glycolysis and reduced mitochondrial respiration in *BAP1*-heterozygous individuals [86].

However, a separate study employing an inducible *Bap1* knockout mouse model did not fully recapitulate this glycolytic shift [87]. While these authors observed reduced mitochondrial protein expression in pancreatic tissue, reminiscent of a Warburg phenotype, they did not detect increased glycolysis or lactate secretion. Instead, these mice displayed additional metabolic alterations including enhanced cholesterol biosynthesis, disrupted lipid metabolism, and impaired gluconeogenesis. These discrepancies may reflect differences in tissue type, sampling methods, or experimental design. Nevertheless, both studies support the broader interpretation that BAP1-deficiency leads to significant metabolic rewiring.

The cholesterol biosynthesis and mevalonate pathways might be promising targets to therapeutically exploit these metabolic vulnerabilities (Fig. 1e). A recent CRISPR-Cas9 kinase knockout screen identified key vulnerabilities in these metabolic pathways in *BAP1*-deficient mesothelioma cells [55]. Follow-up experiments revealed that combining the mevalonate pathway inhibitor

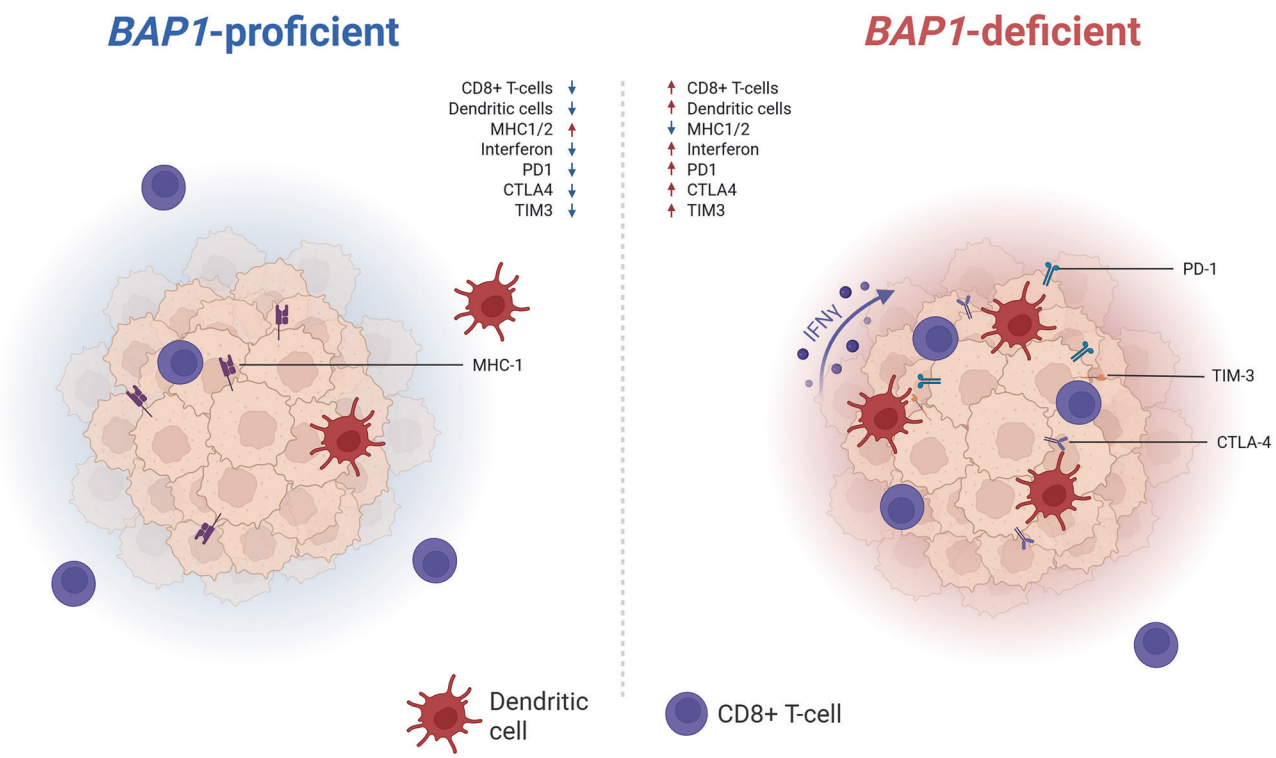

Fig. 2 Immune landscape of BAP1-proficient versus BAP1-deficient mesothelioma. BAP1-proficient mesotheliomas (left) typically show limited immune infiltration, with fewer CD8⁺ T-cells and dendritic cells, reduced MHC-I/II expression, and lower interferon signaling. Immune checkpoint molecules such as PD-1, CTLA-4, and TIM-3 are expressed at low levels. By contrast, BAP1-deficient mesotheliomas (right) display an inflamed tumor microenvironment characterized by increased CD8⁺ T-cell and dendritic cell infiltration, higher interferon activity, and upregulation of immune checkpoint molecules (PD-1, CTLA-4, TIM-3). These features suggest enhanced immunogenicity, although clinical evidence linking BAP1 status to immune checkpoint blockade response remains limited.

zoledronic acid with the EZH2 inhibitor tazemetostat significantly reduced tumor volume and improved overall survival in an autochthonous *BAP1*-deficient mesothelioma mouse model [26], warranting further evaluation in prospective clinical trials.

BAP1-loss may predict efficacy of ASS1 inhibitors. Arginine-depleting agents such as pegargiminase have shown modest but statistically significant efficacy in mesothelioma. The recent ATOMIC-meso phase III trial in non-epithelioid mesotheliomas reported a median overall survival of 9.3 months (95% CI: 7.9–11.8) for pegargiminase combined with chemotherapy, compared with 7.7 months (95% CI: 6.1–9.5) for placebo with chemotherapy [88]. Although this trial did not stratify patients based on genetic alterations, a recent cell line study suggested that *BAP1*-loss may enhance *ASS1* expression, potentially increasing sensitivity to ASS1-targeted inhibitors [89]. These findings highlight the need for evaluating *BAP1* status as a potential biomarker in arginine-depletion treatment strategies.

BAP1-loss as a predictive biomarker for immunotherapy

Immune checkpoint blockade for mesothelioma patients. Immune checkpoint blockade (ICB) with nivolumab plus ipilimumab was recently approved for the first-line treatment of pleural mesothelioma, based on results from the phase III CheckMate 743 trial [90]. This drug combination demonstrated improved overall survival in a subset (~40%) of patients, particularly in those with non-epithelioid histology (18.1 vs. 8.8 months; HR: 0.46; 95% CI: 0.31–0.68). In contrast, among patients with epithelioid histology, immunotherapy did not significantly outperform standard platinum-based chemotherapy (18.7 vs. 16.5 months; HR: 0.86; 95% CI: 0.69–1.08). While histological subtype and *PD-L1* expression can be used to guide treatment decisions, it remains unclear whether specific genomic alterations, such as *BAP1*-loss, are predictive of ICB response in pleural mesothelioma. Several studies have explored how *BAP1* status may affect the tumor immune microenvironment in both pleural and peritoneal mesothelioma [91–94] (Fig. 2), although direct clinical evidence linking *BAP1* status to ICB outcomes remains limited to case reports and a small retrospective study [95–98].

BAP1-loss and composition the tumor immune microenvironment. A multi-omics study in 19 treatment-naïve peritoneal mesotheliomas found that loss or inactivation of one *BAP1* allele (*BAP1* haploinsufficiency) was associated with a mixed immune phenotype: *BAP1*-haploinsufficiency correlated with reduced expression of adaptive immune and MHC-I/II antigen presentation genes, but increased expression of genes related to the innate immune system, cytokine signaling, Toll-like receptor pathways, the interferon response, and several immune checkpoint genes including *CTLA4*, *PD1*, and *TIM3* [91]. These findings were interpreted as indicative of increased susceptibility to ICB, despite the reduced expression of adaptive immune gene signatures. Supporting this, a multiplex immunohistochemistry study of 88 pleural and 25 peritoneal mesotheliomas reported increased infiltration of cytotoxic CD8+ T-cells and dendritic cells in *BAP1*-deficient tumors [92]. Tumor-T-cell interactions were also more frequent in these cases, suggesting a more inflamed tumor microenvironment. Similarly, a transcriptomic analysis of the TCGA ($n = 86$) and MSK-IMPACT ($n = 61$) datasets found that mesotheliomas harboring *BAP1*-loss in the absence of co-alterations in *CDKN2A/B* or *NF2* exhibited higher expression of gene signatures associated with response to anti-PD-1 therapy [93]. Another transcriptomic analysis using the TCGA ($n = 87$) and E-MTAB-1819 ($n = 33$) cohorts, which was also validated in two independent

datasets ($n = 17$ and $n = 98$), reported modest increases in interferon alpha/gamma pathway activity and immune checkpoint gene expression in *BAP1*-deficient tumors [94]. However, no major differences in adaptive immune cell infiltration were observed. In line with prior immunohistochemistry studies [92], this analysis also found that tumor-T-cell proximity was greater in *BAP1*-low tumors.

BAP1-loss and the clinical efficacy of immunotherapy. Only limited evidence is available on the impact of *BAP1*-loss on immunotherapy efficacy in real-world clinical settings. A retrospective analysis of 45 pleural mesothelioma patients (*BAP1*-deficient: 8; *BAP1*-wildtype: 6; *BAP1*-untested: 31) found no significant differences in objective response rate or median progression-free survival between *BAP1*-deficient and *BAP1*-wildtype/untested patients treated with immune checkpoint blockade [95]. In contrast, while several case reports of *BAP1*-deficient mesothelioma patients treated with ICB have shown promising results (see e.g., refs. [96, 97]), extrapolation from these case reports is problematic due to potential selection bias and lack of standardized follow-up.

Taken together, these findings suggest that *BAP1*-loss may be associated with a more inflamed and immunologically active tumor microenvironment, although clinical evidence linking *BAP1* status to ICB response remains limited. Retrospective analyses of ICB-treated cohorts and prospective trials stratified by *BAP1* status will be required to determine whether it can serve as a reliable biomarker for immunotherapy response in mesothelioma.

BAP1-loss as a predictive biomarker for chemotherapy

Platinum-based chemotherapy remains a key treatment option for mesothelioma patients, especially for those with epithelioid histology, in whom immune checkpoint blockade does not provide significant survival benefits compared to chemotherapy [30, 90]. The standard regimen of cisplatin/carboplatin combined with pemetrexed yields a median overall survival of ~12 months, with an objective response rate ranging from 20 to 50% [98]. The addition of angiogenesis inhibitors such as bevacizumab can further improve median overall survival to ~15–19 months [98]. Moreover, for patients that progress on first-line immune checkpoint blockade, chemotherapeutic agents such as gemcitabine, vinorelbine, and ramucirumab remain important second- and third-line options [30].

Several retrospective studies have evaluated the association between *BAP1* status and chemotherapy response [99–101]. An analysis of 150 pleural mesothelioma patients across two cohorts treated with either platinum plus pemetrexed or best supportive care found that *BAP1*-deficient tumors were more sensitive to chemotherapy, with a significantly improved overall survival compared to *BAP1*-wildtype tumors (20.2 vs. 7.3 months; $p < 0.001$, and 19.6 vs. 11.1 months; $p < 0.01$, respectively) [99]. In contrast, a smaller retrospective study of 87 pleural mesothelioma patients reported the opposite trend, finding that *BAP1*-deficient tumors were less responsive to platinum-based chemotherapy [100]. While the authors speculated that this could reflect impaired chemotherapy-induced apoptosis in *BAP1*-deficient tumors, their analysis was limited to objective response rate and did not assess overall survival. This limitation may partially explain the conflicting results.

Vinorelbine is an alternative chemotherapy option that functions through microtubule-disruption, and has been evaluated in the context of *BAP1* status. A retrospective analysis of 60 patients treated with active symptom control (ASC) plus vinorelbine found that *BAP1*-negative patients exhibited a non-significant trend toward improved survival (HR: 0.21; 95% CI: 0.04–1.06; $p = 0.06$) [101]. This interaction between BAP1-loss and sensitivity to microtubule disruptors might be explained by BAP1's role in the spindle assembly checkpoint, regulation of spindle length, and growth of astral microtubules [72].

While these findings suggest a possible predictive role for *BAP1* status in chemotherapy-treated mesothelioma, the evidence remains inconsistent. Conflicting results across retrospective studies, differences in endpoints (e.g., ORR vs. OS), and limited cohort sizes underscore the need for prospective trials stratified by *BAP1* status to clarify its value as a treatment biomarker.

CONCLUSIONS

While the molecular functions of BAP1 such as chromatin regulation, DNA damage response, and cellular metabolism have been well characterized in preclinical studies, translating these findings from model systems into effective therapies for patients has proven challenging. Recent clinical trials evaluating targeted therapies such as EZH2 inhibitors (e.g., tazemetostat), PARP inhibitors (e.g., olaparib), and FGFR inhibitors (e.g., AZD4547) have shown limited efficacy and specificity in *BAP1*-deficient mesothelioma, despite strong mechanistic rationale from preclinical studies.

Emerging combination strategies, such as dual inhibition of EZH2 with ATM, FGFR, or mevalonate pathway targets, have demonstrated synergistic anti-tumor effects in preclinical models, but remain untested in human studies. These approaches warrant further investigation in biomarker-stratified prospective clinical trials. Since clear biological differences have been observed between germline and somatic *BAP1*-alterations in mesothelioma, this status should be explicitly reported upcoming clinical studies.

In parallel, growing evidence suggests that *BAP1* alterations may shape the tumor immune microenvironment, with some studies reporting increased T-cell infiltration and upregulation of immune checkpoint molecules. However, evidence for a direct association between *BAP1* status and clinical response to immune checkpoint blockade is currently absent. Similarly, while retrospective studies have suggested a potential link between *BAP1*-status and chemotherapy sensitivity, these findings remain conflicting and have yet to be validated in prospective trials.

In summary, *BAP1*-loss is a defining molecular feature of mesothelioma, with significant diagnostic and mechanistic implications for mesothelioma biology. Bridging the gap between mechanistic insights and therapeutic applications remains a major challenge, and will be essential for the development of more effective, personalized treatment strategies for this hard-to-treat cancer.

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AUTHOR CONTRIBUTIONS

JHLT van Genugten conceived the review, performed the literature search, synthesized the information, and drafted the manuscript. DA Fennell and P Baas provided critical revision of the manuscript. All authors reviewed and approved the final manuscript.

COMPETING INTERESTS

JHLTvG declares no competing interests. DAF reports grants from Aldeyra, Astex Therapeutics, Bayer, BMS and Boehringer Ingelheim, Owkin; non-financial support from BerGenBio, Clovis, Eli Lilly, MSD, Roche, and Tesaro GSK; personal fees from Aldeyra, Cambridge Clinical Laboratories, Ikena, Opna Bio, Owkin, RS Oncology, Roche, MSD. PB reports institutional payments and grants: study grants from BMS, Pfizer, and Roche; consultant and advisory services for MSD, BMS, Aduro, BoehringerIngelheim, Targovax and Verastem.

ADDITIONAL INFORMATION

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