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State of the Art: Advances in Malignant Pleural Mesothelioma in 2017

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Key Words: mesothelioma, immunotherapy, BAP1, mesothelin, surgery, radiation, review, therapy

Conflicts of interest:

A. Dr. Amanda McCambridge has no conflicts of interest to disclose.
B. Dr. Andrea Napolitano has no conflicts of interest to disclose.
C. Professor Dean Fennell reports personal fees and other non-financial support from Roche, BMS Epizyme, and Astra Zenica. He also reports receiving grants, personal fees and other non-financial support from Boehringer Ingelheim, personal fees from Abbvie, and other non-financial support from MSD. These are not relevant to the submitted work. Professor Fennell also reports serving on the Advisory Boards for Roche, Epizyme, BMS, Abbvie, and Boehringer Ingelheim, as well as acting as serving on the speaker bureau for Astra Zenica, MSD, Boehringer Ingelheim, and Roche, for which honoraria have been granted.
D. Dr. Aaron Mansfield reports serving on the Genentech Advisory Board and the AbbVie Advisory Board, for which honoraria were granted to his institution. Furthermore he reports research funding to his institution from Novartis. These are not relevant to the submitted work.
E. Dr. Yoshitaka Sekido reports grants from Kyowa Hakko Kirin Co, Ltd, and Eisai Co, Ltd which are not relevant to the submitted work.
F. Professor Nowak reports grants from Astra Zeneca, and personal fees from Boehringer Ingelheim, Roche International, Epizyme, Merck, and Bristol Myer Squibb. These are not relevant to the submitted work.
G. Professor Reungwetwattana has no conflicts of interest to disclose.
H. Dr. Mao has no conflicts of interest to disclose.
I. Dr. Harvey Pass has a patent for Fibulin 3 pending, a patent regarding Osteopontin licensed to Wayne State University, and a patent regarding HMGB1 licensed to University of Hawaii.
J. Dr. Michele Carbone: To be submitted separately
K. Dr. Tobias Peikert reports serving on the Epizyme Advisory Board, for which an honorarium was granted to his institution. This relevance lies outside the submitted work.
L. Dr. Haining Yang reports grants from NCI, grants from DoD, grants from V Foundation, grants from United-4 A Cure Foundation, grants from Mesothelioma Applied Research Foundation,
grants from Hawaii Community Foundation, during the conduct of the study. In addition, Dr. Yang has a patent for a Biomarker of Asbestos Exposure and Mesothelioma (Patent No: US 9,244,074 B2), a patent for Methods and Kits for Analysis of HMGB1 Isoforms, and has filed a US Provisional Patent application (no. 62/106,092) which is pending, and a patent for Treatment and Prevention of Cancer with HMGB1 Antagonists (US Application no. 14/123,607) which is pending.
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Abstract:

Malignant pleural mesothelioma (MPM) is an uncommon, almost universally fatal, asbestos-induced malignancy. New and effective strategies for diagnosis, prognostication and treatment are urgently needed. Herein we review the advances in MPM achieved in 2017. While recent epidemiological data demonstrated that the incidence of MPM-related death continued to increase in United States between 2009 and 2015, new insight into the molecular pathogenesis and the immunological tumor microenvironment of MPM, for example, regarding the role of BRCA1 associated protein 1 (BAP1) and the expression programmed death receptor ligand 1 (PD-L1), are highlighting new potential therapeutic strategies. Furthermore, there continues to be an ever-expanding number of clinical studies investigating systemic therapies for MPM. These trials are primarily focused on immunotherapy using immune checkpoint inhibitors alone or in combination with other immuno- and non-immuno therapies. In addition, other promising targeted therapies including ADI-PEG20 focusing on argininosuccinate synthase 1 deficient tumors and Tazemetostat, an EZH2 inhibitor of BAP1 deficient tumors are currently being explored.
Introduction and Background

Malignant pleural mesothelioma (MPM) is a rare aggressive neoplasm, closely linked to asbestos exposure. Median survival ranges between 6-8 months for patients treated with best supportive care and 12-16 months with pemetrexed-containing systemic cytotoxic therapy\(^1\). Therapy is generally palliative, improving symptoms and modestly increasing survival\(^2, 3\). While asbestos control regulations significantly decreased occupational exposure, many individuals remain at risk\(^3, 4\). Asbestos is the commercial name used to identify six different commercially used fibers, however there are over 400 asbestiform fibers in nature, and many have been proven to be carcinogenic, including erionite, and antigorite\(^5\). The Centers for Disease Control (CDC) identified 45,221 MPM-related deaths in the United States (US) between 1999-2015, with a 4.8% increase in MPM deaths over this period, which was seen across all ethnicities\(^4\). Furthermore, Eastern Europe and other rapidly industrializing regions, where asbestos production and commercial use continues unregulated, may experience an increased incidence of MPM in coming decades\(^6-8\). Fewer MPM cases have been reported from East and Southeast Asia. It is hypothesized that this is secondary to a more recent industrialization and that numbers in these regions will start to rise in years to come\(^9, 10\). The ongoing increase in mortality related to MPM underscores the urgent need for asbestos control, improved understanding of the disease pathogenesis, early detection and better treatment options.

Research output in this field has been increasing steadily. A comprehensive MEDLINE literature search identified relevant publications in 2017. Based on the expert opinion of the authors we elected and reviewed all publications relevant to the epidemiology, pathology, genomics, diagnosis, staging and therapy of MPM published in 2017. In addition, we reviewed and included relevant abstracts of ongoing or recently completed MPM clinical trials presented at 2017 ASCO, 2017 ESMO and the 2017 World Congress of Lung Cancer.
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**Lessons in Epidemiology and Occupational Medicine**

Intra-individual biopersistence of asbestos fibers over time was analyzed in 12 longitudinally collected human lung tissue samples. The results suggested that the purportedly less carcinogenic chrysotile asbestos fibers also demonstrate a long biopersistence, and therefore likely account for a proportion of MPM cases\(^1\), confirming suggestions by pre-clinical studies\(^2\). A second large study provided insights into the dose-time-response relationship between occupational asbestos exposure and pleural mesothelioma, suggesting that initial high doses of asbestos, followed by low doses thereafter are associated with the highest risk \(^3\). Moreover, non-occupational asbestos exposure is an increasingly recognized risk factor for MPM. In this context a recent review and meta-analysis supported the critical need to evaluate MPM risk in communities with ambient asbestos or other carcinogenic fiber exposures\(^4\). Finally, in a large study across 230 countries over a 20 year period, the global burden of MPM deaths was extrapolated to about 38,400 per year, suggesting that it might be even higher than the most recently reported values\(^5\).

**Developments in Diagnosis and Staging**

Blood-based biomarkers serve several potential roles in MPM: diagnostic, prognostic, or predictive of response to specific therapies. The most studied blood-based biomarkers are mesothelin, osteopontin, fibulin-3\(^6\), and HMGB1\(^7\). In 2017, three meta-analyses respectively confirmed that pretreatment thrombocytosis\(^8\), elevated neutrophil-to-lymphocyte ratio\(^9\), and high serum levels of soluble mesothelin\(^10\) are prognostic for poor survival. A recent study identified complement component 4d as a promising biomarker correlating with tumor volume, response to chemotherapy, and survival\(^11\). Other potentially useful blood based diagnostic markers for mesothelioma include midkine, calretinin and
miRNA\textsuperscript{22, 23,24, 25}. Deregulated miRNA levels of Let-7c-5p and miR-151a-5p in tissue may also be prognostic in MPM\textsuperscript{26}. In addition, proteomic analysis of the secretome, including exosomes from MPM cells identified proteins that potentially enhance the growth and stress response, and inhibit adaptive immunity\textsuperscript{27, 28}.

Clinical and pathological staging is important to determine disease prognosis and facilitate patient selection for multi-modality therapy. The IASLC Mesothelioma Staging Project for the 8\textsuperscript{th} edition of the AJCC/UICC staging manual updated TNM staging in MPM\textsuperscript{29-31}. However the project database still overrepresented surgically treated patients and, despite recent advances in cross-sectional anatomic and functional imaging, and mediastinal lymph node sampling, clinical staging remains difficult. One challenge is the inability to distinguish tumor tissue from surrounding normal tissues for staging and follow-up using standard anatomic cross-sectional imaging. While the current version of the modified RECIST guidelines for MPM is more applicable to mesothelioma than RECIST 1.0 or 1.1, further research-based optimization of response criteria for MPM is still required. Tumor volume is increasingly recognized as an anatomical, imaging-based prognostic factor, however valid and reliable measurement of this parameter across sites and software platforms is difficult\textsuperscript{32}. Attempts to create an automated volumetric assessment of tumor volume for treatment response and prognostication have been difficult due to a lack of accuracy and reproducibility\textsuperscript{33-42}. The most promising results on the prognostic value of CT-based tumor volume were recently published from a multi-institutional group\textsuperscript{43, 44}. de Perrot and colleagues published data suggesting that lower radiological tumor volume and smaller diaphragmatic tumor thickness predicted favorable outcomes in patients treated with neoadjuvant radiation followed by extra-pleural pneumonectomy (EPP)\textsuperscript{45, 46}. In addition, a group from the UK also reported a promising random walk-based computer-aided algorithm for image segmentation\textsuperscript{47}.
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**Progresses in Pathology**

The histological diagnosis of MPM is relatively well established when performed by expert pathologists, based on positive markers of mesothelial lineage and negative markers of epithelial lineage. However, diagnostic uncertainty remains common, and continued efforts to improve the accuracy of diagnosis are needed\(^4^8\). One of the most challenging differential diagnoses remains the distinction between sarcomatoid MPM and sarcomatoid carcinoma of the lung. In this respect, MUC4 may be a novel sensitive and specific immunohistochemical biomarker for sarcomatoid carcinoma of the lung\(^4^9\). Moreover, GATA3 immunostaining may be useful to identify sarcomatoid and desmoplastic mesothelioma\(^5^0,5^1\). Disabled homolog 2 (DAB2) and Intelectin-1 were reported as new positive immunohistochemical markers for epithelioid mesothelioma\(^5^2\).

Another challenging differentiation has been between MPM and reactive mesothelial hyperplasia (RMH). While BAP1 immunohistochemistry and p16 FISH can effectively discriminate MPM from RMH, methylthioadenosine phosphorylase (MTAP) loss may also be useful when identified in combination with BAP1 loss\(^5^3\).

In addition, several studies have focused on the evaluation of biomarkers of immunological activation and infiltrating immune cells, in particular, PD-L1\(^5^4-5^7\). The “don’t eat me” signal CD47 was also shown to be overexpressed in diffuse malignant mesothelioma, and was suggested as a potential diagnostic and therapeutic target of MPM\(^5^8\).

**Molecular Advances**

Previous genomic analysis identified the loss of various tumor suppressor genes as the most common molecular event in MPM. Commonly inactivated tumor suppressor genes include the cyclin-dependent kinase inhibitor 2A (CDKN2A), BRCA1 associated protein 1 (BAP1), neurofibromin 2 (NF2), and occasionally TP53. These findings have been confirmed in a recent comprehensive genomic analysis.
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(Figure 1) Enhanced understanding of MPM molecular aberrations has already informed the use of targeted therapies such as the FAK inhibitor (Defactinib) for tumors lacking NF2 (COMMAND study). Unfortunately, maintenance defactinib did not improve patient outcomes and the study was terminated early. A recent publication provides a comprehensive review of molecular advances in MPM.

The role of heredity in familial MPM predisposition, even without occupational asbestos exposure, has finally been proven by the discovery of germline BAP1 mutations, and supported by murine modeling. As a result, the tumor predisposing BAP1 cancer syndrome has been increasingly recognized and characterized. BAP1 is a deubiquitinating enzyme with several roles in regulating DNA repair and gene expression. In addition to germline mutations predisposing to mesothelioma and other cancers, BAP1 is the most frequent acquired (somatic) mutation in sporadic mesothelioma. In 2017, both pleural and peritoneal mesotheliomas were shown to have loss of BAP1 in more than 60% of cases, confirming previous findings. Novel functions of BAP1 which likely contribute to its role in cancer in general, and in MPM in particular, have been identified. Specifically, BAP1 is a master regulator of calcium-induced apoptosis via regulation of the IP3R3 receptor ubiquitination, as well as of cellular glycolytic metabolism, and a radical of oxygen homeostasis. A novel alternative splice isoform of BAP1 that misses part of the catalytic domain has also been described, and it appears to regulate DNA damage response and influence drug sensitivity. Furthermore, frequent germline mutations in other genes associated with DNA repair have been identified in asbestos-exposed individuals who developed MPM, suggesting theses pathways to be associated with MPM predisposition. Interestingly common germline BAP1 variants appear to mediate the risk of developing renal cell carcinoma and lung cancer, and possibly also MPM. When mesothelioma develops in carriers of germline BAP1 mutations, these malignancies have a much better prognosis, and survival of 5 or more years is commonly seen.
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In 2017 the role of \textit{BAP1} immunohistochemistry in MPM diagnosis and possibly prognosis has also been the focus of several studies. Specifically, \textit{BAP1} loss has been shown to reliably differentiate MPM from chronic pleuritis, benign mesothelial hyperplasia and other benign mesothelial lesions, as well as from other malignancies such as non-small cell lung cancer and ovarian serous tumors\textsuperscript{53, 79-83}.

The identification of hereditary factors in MPM pathogenesis has also led to increased interest in the characterization of young patients. In 2017 it was reported that these patients show distinctive clinical, pathologic and genetic features, such as: higher likelihood of a past history of mantle radiation, family history of breast cancer, and lower rates of \textit{CDKN2A} deletion than older patients\textsuperscript{84}. Moreover, a subset of mesotheliomas in young patients (15%), were associated with recurrent \textit{EWSR1/FUS-ATF1} fusions\textsuperscript{85}. Most importantly, the presence of clinically actionable ALK rearrangements was described in about 10\% of peritoneal mesothelioma, most commonly younger women\textsuperscript{86}.

\textbf{Systemic Therapies}

\textit{Targeting Angiogenesis:}

Systemic cytotoxic chemotherapy with pemetrexed plus cisplatin remains the only FDA approved therapy for MPM and represents the current standard of care. With treatment response rates of approximately 40\% it extends median overall survival to 12-16 months\textsuperscript{87}. As VEGF signaling is important in the pathophysiology of MPM, VEGF inhibition is being explored as a potential treatment option\textsuperscript{88-91}. The results of the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) demonstrated a statistically significant improvement in overall survival when bevacizumab was added to first-line cisplatin and pemetrexed chemotherapy\textsuperscript{92}. However due to the observed relatively small increase in overall survival, the addition of bevacizumab to chemotherapy has not become standard of care in most parts of the world, and is recommended as optional in the National Cancer Center Network (NCCN)
Mesothelioma 2017 guidelines\(^92\). A cost-effectiveness analysis published in 2017 did not support the addition of bevacizumab\(^93\).

Another antiangiogenic, nintedanib, is a small molecule tyrosine-kinase inhibitor targeting VEGF receptors, fibroblast growth factor receptors (FGFR), and platelet derived growth factor receptors (PDGFR). The LUME-MESO study is an ongoing randomized, double blind, placebo-controlled Phase II/III examining the efficacy and safety of adding nintedanib to standard chemotherapy in non-surgical MPM patients; phase II results were reported in 2017\(^94\). In 87 evaluable patients (44 nintedanib, 43 placebo), nintedanib improved progression-free survival (PFS) by 3.7 months as compared with placebo (p=0.01), most notably in those with epithelioid histology (4 months PFS, p=0.006). There was a trend towards improved overall survival (OS) (median 18.3 months versus 14.2 months) in favor of the nintedanib group, however this difference was not statistically significant; the study was not powered to examine OS. The addition of nintedanib to standard chemotherapy was safe, and these results support the rationale for the ongoing Phase III study\(^94,95\) (Table 1).

**Blocking Immune checkpoints:**

In 2017 immunotherapy was clearly the focus of the largest number of clinical trials investigating new therapies for MPM. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is expressed on T cells, reducing the amplitude of CD28-mediated T cell activation\(^96\). CTLA-4 inhibition enhances T-cell activation and increases antitumor efficacy in other cancers\(^97\). Phase II studies investigating Tremelimumab, a selective human monoclonal antibody against CTLA-4, showed favorable PFS responses and toxicity profiles\(^98,99\). In 2017, the double-blind study comparing Tremelimumab to placebo in subjects with previously treated unresectable malignant mesothelioma (DETERMINE)
disappointingly failed to demonstrate differences in OS or PFS between the treatment and control
groups\textsuperscript{100} (Table 2).

The characterization of the immunological tumor microenvironment has been the subject of
considerable research, and the immune status of MPM has been distinctly correlated to prognosis\textsuperscript{101, 102}.
Approximately 60\% of MPM either expressed PD-L1 or displayed an “inflamed status” designated by a
specific mRNA signature, indicating potential susceptibility to immune-directed therapy\textsuperscript{103, 104}. Human
monoclonal antibodies against PD1 and PD-L1 are approved for multiple malignancies including first line
therapy for non-small cell lung cancer alone for tumors with \( \geq 50\% \) PD-L1 staining\textsuperscript{105, 106}, or in
combination with chemotherapy regardless of PD-L1 staining for adenocarcinoma\textsuperscript{107}. There are many
ongoing clinical trials investigating PD1/PD-L1 checkpoint inhibitors alone and in combination.

**Single agent immunotherapy trials**

Between 20-40\% of MPM patients express PD-L1 at various levels, and PD-L1 expression correlates with
a poorer prognosis\textsuperscript{103, 108}. In the KEYNOTE-028 trial, the efficacy and safety of pembrolizumab as
subsequent line therapy was evaluated in 25 patients with PD-L1 positive MPM (\( \geq 1\% \) PD-L1 positivity)\textsuperscript{109}.
Twenty percent of patients achieved a partial response, and 52\% demonstrated stable disease, with a
12-month median duration of response. Furthermore, the median PFS (5.4 months) and the median OS
(18 months) were notably longer than patients not receiving second-line therapy. PD-L1 positivity and
level of expression were not clearly linked to likelihood of clinical response\textsuperscript{109}. The Netherlands Cancer
Institute is currently conducting a similar phase II trial of a PD1 inhibitor, nivolumab, in relapsed MPM
patients. Preliminary results reported a disease control rate of 50\% at 12 weeks, and 33\% at 24 weeks,
with a median PFS of 3.6 months\textsuperscript{110}. Avelumab, an anti-PD-L1 antibody also demonstrated clinical
activity against MPM in the JAVELIN study, with a response rate of 9.4\% and stability in 47\%, and median
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PFS of 4.3 months\(^\text{111}\). Similar results have been reported from a phase II trial of Pembrolizumab\(^\text{112}\), and
the Nivolumab MERIT study\(^\text{113}\).

The ongoing Phase III CONFIRM study randomizes patients requiring second line therapy to nivolumab or placebo (NCT03063450). The PROMISE-Meso study, comparing pembrolizumab to gemcitabine or vinorelbine in pre-treated, nonsurgical MPM patients is also currently recruiting (NCT02991482).

Immunotherapy combination trials

In 2017, preliminary findings have also been reported of several ongoing studies investigating combination immune checkpoint inhibition pairing anti-PD1/L1 therapy with anti-CTLA-4 therapy. Preliminary results of the NIBIT-MESO (tremelimumab and durvalumab)\(^\text{114}\), MAPS-2\(^\text{115}\) and INITIATE (both ipilimumab and nivolumab)\(^\text{116}\) trials demonstrate potential efficacy for second line therapy of mesothelioma. MAPS-2 is a Phase II study including 108 evaluable patients treated with nivolumab versus nivolumab plus ipilimumab. While the results of the nivolumab arm were promising, the 54 patients in the combination arm had a higher DCR (51.6%), although three treatment-related deaths were also reported\(^\text{115}\). Sixty percent of patients in the NIBIT-MESO trial experienced adverse events, with three patients requiring study discontinuation due to treatment-related toxicity\(^\text{114}\). INITIATE appears to be the most favorable thus far based on preliminary data from a 12 week analysis, with a DCR of 72% and only 29% of patients who have experienced grade 3 or 4 toxicity\(^\text{116}\). Checkmate 743 is an ongoing randomized controlled Phase III study comparing the combination of ipilimumab and nivolumab with pemetrexed/cisplatin as first line therapy in 600 patients, and is approaching completion of enrolment\(^\text{117}\).

Further studies are addressing combinations of anti-PD1/L1 therapy with chemotherapy. The DREAM study is evaluating the effect of durvalumab (anti-PD-L1) plus standard chemotherapy followed by durvalumab alone and has completed recruitment\(^\text{118}\). Other similar studies, such as CCTG
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(cisplatin/pemetrexed versus cisplatin/pemetrexed plus pembrolizumab; NCT02784171), PrECOG (Durvalumab + cisplatin/pemetrexed; NCT02899195), and SWOG (cisplatin/pemetrexed plus Atezolizumab and surgery; NCT03228537) are recruiting (Table 3).

Based on recent evidence suggesting a role for focal adhesion kinase in the regulation of the immunosuppressive microenvironment\textsuperscript{119}, and synergy between FAK and PD1 inhibition\textsuperscript{120}, a proof of concept phase 1b/2A clinical trial of pembrolizumab and FAK is ongoing and includes a mesothelioma cohort (NCT02758587).

While PD1/PD-L1 targeted checkpoint inhibition has demonstrated promising clinical responses in early phase studies, the results of the ongoing Phase III studies described are needed to better define the role of this approach. It is unclear whether the potentially small additional benefit of combination immune checkpoint inhibition will justify the increased toxicity.

Promising Targeted Therapies:

**BAP1 Loss in MPM**

*BAP1* plays an independent role in epigenetic regulation and malignant transformation. *BAP1* loss results increased trimethylated histone H3 lysine 27 (H3K27me3), elevated enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) expression, and enhanced repression of polycomb repressive complex 2 (PRC2) targets. In preclinical models EZH2 inhibition has been shown to be beneficial in MPM with *BAP1* loss\textsuperscript{121} (Figure 1). A Phase II clinical trial investigating the EZH2 inhibitor tazemetostat in MPM completed enrollment and results should be available soon (NCT02860286). *BAP1* inactivation alters double strand DNA repair via homologous recombination\textsuperscript{122, 123}. However, the potential implication for poly ADP ribose polymerase (PARP) inhibitor sensitivity in mesothelioma have not yet been evaluated, although the MiST 1 study is currently in development in the UK.
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Targeting Mesothelin

Mesothelin is a cell surface glycoprotein expressed on cells lining the pleura, peritoneum, pericardium, as well as on MPM cancer cells\textsuperscript{124, 125}. It is an attractive potential target in MPM due to its high surface expression\textsuperscript{126, 127} and its suspected involvement in tumorgenesis\textsuperscript{128}. Mesothelin-targeted therapies involving antimesothelin immunotoxins (SSP1), chimeric anti-mesothelin antibodies (amatuximab), mesothelin-directed antibody drug conjugates (anetumab ravtansine), Listeria based vaccines (CRS-207) and chimeric antigen receptor expressing T-cells (CAR-T-cells) have shown some promise in early phase studies\textsuperscript{129} (Figure 2), and further studies are ongoing. The recently reported randomized, open-label, active-controlled, multicenter superiority phase II study investigating Anetumab ravtansine versus vinorelbine as second line treatment in patients with mesothelin-positive MPM (248 patients) did not show a difference between the treatment groups\textsuperscript{130} (Table 1).

However, there are additional promising preclinical models. Recently, a preclinical study combining direct tumor injection of mesothelin immunotoxin with intra-peritoneal injection of anti-CTLA-4 therapy demonstrated an 86\% complete response (CR) rate of in directly treated tumors and a 56\% CR of a second untreated tumor while no CR occurred when both drugs were given separately\textsuperscript{131}. A similar combination approach was also published using an anti-mesothelin immunotoxin (RG7787) plus nab-paclitaxel (albumin-bound paclitaxel) in mesothelioma cell lines. Three of four lines revealed durable CR, and studies in human patients began in 2017\textsuperscript{132}.

Arginine deprivation therapy

Argininosuccinate synthetase 1 (ASS1) is the rate-limiting enzyme in arginine production, and cell lines deficient of ASS1 usually require exogenous arginine supplementation\textsuperscript{133} (Figure 3). Intratumoral ASS1 deficiency has been identified in 63\% of archived mesothelioma lines, and is associated with increased tumorgenesis, and more aggressive disease\textsuperscript{133-135}. In vitro studies of arginine deprivation with adenosine
deaminase (ADI-PEG20) improve progression free survival, with low toxicity\textsuperscript{136-140}. Szlosarek and colleagues applied this concept to mesothelioma, conducting the first prospective biomarker-driven randomized controlled trial in this disease\textsuperscript{141}. Forty-four patients received ADI-PEG20 plus best supportive care, and 24 patients received best supportive care only, with pre-determined interval imaging to assess for progression of disease. They observed a median PFS of 3.2 months in the treatment group as compared to 2.0 months in the control group (\(p = 0.03\)) (\textbf{Table 2}). These findings led to a Phase I study of ADI-PEG20 combined with standard-of-care chemotherapy in ASS1-deficient mesothelioma and non-small cell lung cancer patients\textsuperscript{142}. Nine patients (5 MPM) received escalating weekly doses of ADI-PEG20 with standard chemotherapy. No dose-limiting toxicities were encountered, and only nine reported adverse events were related to ADI-PEG20, most commonly rash. All patients experienced stable disease, and seven (78\%) achieved a partial response, including one with sarcomatoid MPM. These results suggested co-administration of standard chemotherapy and arginine deprivation therapy in ASS1-negative patients was well tolerated and could improve tumor response over chemotherapy alone\textsuperscript{142}. A phase II/III trial is currently recruiting MPM patients with 75\% loss of ASS1\textsuperscript{143}.

\textbf{NF2 Targeted Therapies}

\textit{NF2} is a gene commonly inactivated in MPM. This gene encodes Merlin, which regulates the Hippo tumor suppressive signaling pathway. Hippo pathway dysregulation leads to constitutive activation of YAP1/TAZ transcriptional coactivators and enhances malignant phenotypes of MM cells\textsuperscript{144}. Although the progress of MPM research based on \textit{NF2} alteration was limited in 2017, novel therapeutic strategies against YAP1/TAZ have been developed for a variety of human malignancies including MPM\textsuperscript{145}. Merlin can also accumulate in the nucleus and suppresses tumorigenesis by inhibiting the cullin E3 ubiquitin ligase CRL4\textsuperscript{DCAF1}. Combining a NEDD8-activating enzyme (NAE) inhibitor, which suppresses CRL4\textsuperscript{DCAF1},
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and mTOR/PI3K inhibitor suppresses the growth of in NF2-mutant mesothelioma and shwannoma cells.\textsuperscript{146}

Other Potential Systemic Therapies

Promising results in the adjuvant setting using the WT-1 peptide vaccine galinpepimut-S after multimodality therapy were shown in a randomized phase II trial, but lacked statistical power to draw stronger conclusions.\textsuperscript{147} Autologous monocyte-derived dendritic cell immunotherapy pulsed with allogenic tumor cell line lysate was effective in mice, and safe in 9 MPM patients in a phase I trial.\textsuperscript{148} A novel therapeutic strategy currently at a preclinical stage for MPM is the inhibition of the pro-tumor alarmin HMGB1 by a number of compounds such as ethyl pyruvate and aspirin.\textsuperscript{149,150}

The antitumoral properties of various viruses have been demonstrated in a number of malignancies.\textsuperscript{151-155} MPM has been the target of many such investigations,\textsuperscript{156} and promising preclinical data regarding adenovirus oncotherapy\textsuperscript{157-160} prompted human studies. HSV-1 oncotherapy has shown dramatic responses in vitro,\textsuperscript{161-163} and preliminary results in human patients revealed a 50% disease stability.\textsuperscript{164} In murine xenografted models of mesothelioma, intrapleural oncolytic vaccinia virus administration resulted in improved 30 day survival.\textsuperscript{165} There have also been several promising studies of MPM and intrapleural administration of oncolytic measles viruses,\textsuperscript{166,167} and a phase I study is ongoing to evaluate efficacy in humans.\textsuperscript{168}

Other promising therapeutic candidates include the monopolar spindle 1 kinase, a kinase of the spindle assembly checkpoint that controls cell division and cell fate;\textsuperscript{169} the mTOR/PI3K/AKT axis for the aggressive subset of MPM harboring simultaneous inactivating mutations of the genes LATS2 and NF2;\textsuperscript{170} the sialylated protein HEG1 which can be targeted by a specific monoclonal antibody;\textsuperscript{171} and
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Targeting of MYC which is upregulated in MPM cells. The first-in-human phase I trial of anti-CD26 antibody, YS110, was also conducted for 33 patients including 22 MPM patients.

Several microRNAs have been reported as potential therapeutic targets with proof of concept in clinical trials, e.g. the microRNA-15/16 family, or the microRNA-137, through its control of YB-1. Interestingly, microRNAs have been shown to contribute to the regulation of PD-L1 expression, opening to novel potential combinations between microRNA-targeting drugs and immune checkpoint inhibitors.

To further bridge preclinical and clinical results, the availability of relevant in vitro and in vivo models is crucial. In this respect, the establishment of primary MPM culture systems to test novel drugs as well as of patient-derived xenografts from pleural mesothelioma represented a significant scientific advance in 2017.

Surgical resection

Optimal treatment of MPM remains controversial, particularly the role of localized therapies such as surgery and radiation. Historically, operable patients underwent EPP, which has significant complications and substantial mortality, with no appreciable benefit to the patient demonstrated by the small randomized MARS pilot study. Pleurectomy/decortication (P/D) was then introduced in an attempt to offer a lung-sparing macroscopic resection of the tumor. Previous uncontrolled studies have suggested that this procedure is associated with fewer adverse events, with equivalent to improved survival benefits. Despite these findings, clinical equipoise regarding the true benefit of either operation remains. In 2017, two large observational studies using the National Cancer Database were conducted. In the first, propensity score matching analysis showed that surgery-based multimodality
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therapy was associated with improved survival and may offer therapeutic benefit among carefully selected patients\textsuperscript{189}. A second study evaluated 271 patients who underwent EPP, and 1036 patients who received P/D. They found no statistically significant differences in OS (19 months in the EPP group and 16 months in the P/D group; \( p=0.120 \)), 30-day mortality (5%, \( p=0.999 \)), or 30-day readmission rates (7% versus 5%; \( p=0.292 \)), implying either technique was a realistic option for surgical candidates\textsuperscript{190}. To further complicate the debate, a relatively large retrospective multicenter study suggested that extended P/D or non-extended P/D (i.e. P/D without resection of the diaphragm and/or pericardium) had similar outcomes in terms of early results and survival rate\textsuperscript{191}. A recently published comprehensive review on quality of life (QoL) in MPM showed that QoL was generally better for patients undergoing P/D compared to EPP\textsuperscript{192}. Presently, the ongoing MARS2 trial is comparing P/D versus no surgery; in 2017 the study surpassed its futility endpoint and patient enrollment will continue\textsuperscript{193}.

**Advances in Radiotherapy**

The ostensible goal of surgery in MPM has been macroscopic complete resection. Surgical resection alone is associated with frequent loco-regional recurrences\textsuperscript{187, 194}, suggesting adjuvant or neoadjuvant radiotherapy (RT) in a multimodality approach may have a role in improving recurrence control. However the role of RT following EPP has been questioned based on a recently published randomized controlled study\textsuperscript{195}.

A systematic review assessing the role of RT following lung sparing surgery (P/D) in MPM\textsuperscript{196} concluded that RT can be delivered safely with encouraging survival data and acceptable levels of toxicity after a lung sparing procedure in MPM. Memorial Sloan-Kettering Cancer Center has been at the forefront of research regarding IMRT after P/D, with studies demonstrating encouraging OS without significant increase in radiation pneumonitis\textsuperscript{197-199}. Shaikh and colleagues evaluated the effect of hemithoracic
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Intensity-modulated radiation therapy (IMRT) compared to conventional RT in patients treated with P/D\textsuperscript{200}. 209 patients were analyzed (131 conventional and 78 IMRT) and demonstrated a statistically improved OS in the IMRT arm (median 20.2 versus 12.3 months, p = 0.001). Notably patients in this arm was also more likely to have achieved a macroscopically complete resection (p=0.01), to have epithelial histology (p=0.003), had higher Karnofsky performance scores upon initial receipt of RT (p=0.01), and were less likely to experience esophagitis (p=0.0007) by multivariable analysis. There were no significant differences in rates of local recurrence\textsuperscript{200}.

Another promising approach has been neoadjuvant high-dose RT to the ipsilateral lung, followed by EPP, pioneered by the Toronto group lead by Drs. de Perrot and Cho. This approach has been shown to be safe and demonstrated a very favorable OS\textsuperscript{201, 202}. This group treated 90 patients between November 2008 and February 2017, with a median survival of 28.3 months for the intention-to-treat population. This approach may be most beneficial in patients with epithelial tumors, low tumor volume and no lymph node metastasis\textsuperscript{45, 195}.

Of note, carriers of germline BAP1 mutations may have a high risk of developing a second malignancy when treated with radiation therapy. Therefore, radiation therapy should be used with caution, similar to the treatment guidelines for patients with Li-Fraumeni syndrome.

**Advances in Palliative Care**

In contrast to lung cancer, a recently reported randomized study did not demonstrate any benefit of early implementation of palliative care for MPM (RESPECT-Meso Study)\textsuperscript{203}. It is worth noting that the RESPECT study was conducted in the United Kingdom and Australia by centers with significant nursing support for patients, and its conclusions do not necessarily negate the potential benefit of palliative care.
in other healthcare settings. In addition, the recently presented PIT Study demonstrated that prophylactic intervention track site radiation did not prevent the occurrence and symptoms of tract site metastasis. The frequency of tract site metastasis was not significantly different; 3.2% in the radiotherapy group and 5.3% in the control group\textsuperscript{204}.

Furthermore, recent data demonstrated that the use of an indwelling pleural catheter resulted in fewer hospital days and fewer subsequent interventions than talc slurry pleurodesis in a randomized study of 144 patients (approximately 25% of patients in each group had MPM)\textsuperscript{205}. It is important to note, however, that clinical concern remains for seeding along a chest tube tract in MPM patients\textsuperscript{206}.

**Conclusion**

The year 2017 was characterized by several important advances in this field, although only a minority would be considered practice changing. As of today, pemetrexed based cytotoxic chemotherapy with or without bevacizumab remains the standard of care for most patients. Immunotherapy trials remain an exciting area of investigation, though it remains unclear if the benefits of combination anti-CTLA-4 and anti-PD-1/L-1 immunotherapy will outweigh the increased risk of toxicity. Many single agent and combination immunotherapy trials are ongoing, and additional results are expected for 2018/19. While physician-directed immune checkpoint inhibitor therapy has now been included into the current NCCN guidelines as an option for second line therapy of MPM, the efficiency of this approach remains unproven, and as such these patients should primarily be encouraged to enroll into ongoing clinical trials.

Improved understanding of MPM molecular biology and the immunological tumor microenvironment provide future therapeutic applications, most notably via the \textit{BAP1} pathway.
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While the role of multimodality therapy including surgery remains controversial, it is encouraging that there are several new approaches and ongoing multicenter studies. The MARS-2 study surpassed its futility endpoint and preliminary findings are expected in the upcoming years. The 2017 advances will hopefully be followed by significant clinical translation and result in the urgently needed improved therapeutic strategies for this devastating disease.
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References:

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153. Xia ZJ, Chang JH, Zhang L, et al. [Phase III randomized clinical trial of intratumoral injection of E1B gene-deleted adenovirus (H101) combined with cisplatin-based chemotherapy in treating squamous
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206. van Ooijen B, Eggermont AM, Wiggers T. Subcutaneous tumor growth complicating the positioning of Denver shunt and intrapleural port-a-cath in mesothelioma patients. *European journal of
Mesothelioma 2017


Table 1: Clinical studies on MPM published in 2017, non-immunotherapy

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<th>Study</th>
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<th>RR%</th>
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These studies were included in the table as they were non-immunotherapy clinical trials on human patients, with some published results in 2017. This is a complete list as of November 2017.
Mesothelioma 2017

*RR = response rate; SD = stable disease; PFS = progression free survival; OS = overall survival; Mo = months; NR = not reported; A = active, not recruiting; R = recruiting

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Table 2: Clinical studies on MPM immunotherapy published in 2017

These studies were included in the table as they were immunotherapy clinical trials on human patients, with some published results in 2017. This is a complete list as of November 2017.

RR = response rate; SD = stable disease; DCR = durable controlled response; PFS = progression free survival; CTLA-4 = Cytotoxic T lymphocyte-associated antigen 4; PD-L1 = programmed death ligand 1; PD-1 = programmed cell death protein 1; NR = not reported; A = active, not recruiting; C = completed; R = recruiting; * = International study not listed in clinicaltrials.gov; (-) = information not available

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Table 3: Clinical studies on MPM; yet to be published
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These studies were included in the table as they are ongoing clinical trials on human patients, but have yet to publish results. This is a complete list as of November 2017.

PD-1 = programmed cell death protein 1; R = recruiting; CTLA-4 = Cytotoxic T lymphocyte-associated antigen 4; C/P = cisplatin/pemetrexed; PD-L1 = programmed death ligand 1; * = International study not listed in clinicaltrials.gov; (-) = information not available.
Mesothelioma 2017

Table 1: Clinical studies on MPM published in 2017, non-immunotherapy

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### Table 2: Clinical studies on MPM immunotherapy published in 2017

These studies were included in the table as they were immunotherapy clinical trials on human patients, with some published results in 2017. This is a complete list as of November 2017.

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Table 2: Clinical studies on MPM immunotherapy published in 2017
Table 3: Clinical studies on MPM; yet to be published

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These studies were included in the table as they are ongoing clinical trials on human patients, but have yet to publish results. This is a complete list as of November 2017.

PD-1 = programmed cell death protein 1; R = recruiting; CTLA-4 = Cytotoxic T lymphocyte-associated antigen 4; C/P = cisplatin/pemetrexed; PD-L1 = programmed death ligand 1; * = International study not listed in clinicaltrials.gov; (-) = information not available
Figure legends:

Figure 1: Genetic alterations in the malignant transformation of MPM and potential therapeutic targets

The NF2 gene encodes the merlin protein, which regulates the Hippo pathway. Loss of NF2 function leads to inactivation of the Hippo pathway, activation of the YAP transcriptional coactivator, ultimately promoting cell proliferation and survival. Defactinib is a focal adhesion kinase (FAK) inhibitor created for potential action on the NF2 pathway, but was unsuccessful in MPM treatment. PTEN is a negative regulator of the PI3K/AKT pathway, and loss of PTEN function results in over activation of this pathway, leading to cell growth and proliferation. BAP1 is a tumor suppressor gene. Without it, the EZH2 component of the PRC2 complex is activated, leading to tri-methylation of Histone 3 Lysine 27 (H3K27), and ultimately malignant transformation. Tazemetostat is an EZH2 inhibitor. CDK2NA encodes p14ARF and p16INK4a. p14ARF interacts with MDM2, resulting in MDM2 degradation and ultimate activation of p53. Loss of p14ARF expression increases MDM2 levels, decreasing p53 function, resulting in increased cell survival. p16INK4a is essential in hyperphosphorylation and subsequent inhibition of the retinoblastoma pathway. Loss of this cyclin-dependent kinase inhibitor leads to unchecked activation of the retinoblastoma pathway and ultimately cell cycle progression. TP53 encodes p53, and loss of this results in loss of p53 and subsequent cell proliferation and survival.
Figure 2: Potential therapeutic targets of mesothelin surface proteins

This figure demonstrates the proposed mechanisms of mesothelioma treatment specifically targeting mesothelin, including via monoclonal antibodies, immunotoxins, antibody drug conjugates, virus-packed vaccine therapy, and CAR-T cell therapy.

TCR = T cell receptor; APC = Antigen presenting cell; CAR = Chimeric antigen receptor; MHC = Major histocompatibility complex
Figure 3: Effect of arginine deprivation on tumor cells

A) In cells with fully functional ASS1, arginine required for the urea cycle can be created from citrulline via the ASS1 enzyme, or via direct uptake from the plasma.  B) In cells deficient in ASS1, its ability to convert citrulline to arginine is decreased at baseline.  ADI-PEG20 is an enzyme that breaks down arginine in the plasma into citrulline and ammonia.  Giving ADI-PEG20 to cells already deficient in arginine further depletes a cell of arginine, inhibiting urea cycle function and eventually leading to cell death.

ASS1 = Argininosuccinate synthetase 1; ASL = Argininosuccinate lyase; NH3 = ammonia