REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Perspectives on the Treatment of Malignant Pleural Mesothelioma

Sam M. Janes, M.D., Ph.D., Doraid Alrifai, M.D., Ph.D., and Dean A. Fennell, M.D., Ph.D.

Malignant mesothelioma is an aggressive tumor arising from the serosal outer linings of the lungs (pleurae), heart, abdomen, and testes. Treatment trials have focused on malignant pleural mesothelioma, which accounts for 90% of cases, is often diagnosed at an advanced stage, and invariably leads to death. Malignant pleural mesothelioma has proved to be a formidable challenge for clinicians and scientists, with the 5-year survival rate continuing to languish at 5 to 10%.[1] By far the most important risk factor for the development of malignant mesothelioma is asbestos exposure, although other risk factors, including related minerals, are beginning to emerge.[2] The United States and other Western countries are seeing a gentle decline in cases of malignant mesothelioma as a result of transforming work practices. In the United States, age-adjusted mortality has been reduced from almost 14 deaths per 1 million persons in 2000 to 11 deaths per 1 million in 2015.[3] Britain (England, Scotland, and Wales) has one of the highest death rates in the world at 77 deaths per 1 million (from 2017 to 2019), although this rate is also in decline.[4] However, regional successes in prevention through eliminating clinically significant exposure to asbestos have not been matched by the development of new treatments.

In this review, we reflect on the limited effect of the few positive phase 3 randomized, controlled studies, as well as recent trials examining the benefit of immunotherapy. We speculate about how rapid advances in our understanding of the genetics and biology of malignant pleural mesothelioma could translate into more effective therapies.

From the Lungs for Living Research Centre, UCL Respiratory, University College London (S.M.J., D.A.), the Department of Thoracic Medicine, University College London Hospital (S.M.J.), London, and the University of Leicester, Leicester (D.A.F.) — all in the United Kingdom. Address reprint requests to Dr. Janes at Lungs for Living Research Centre, UCL Respiratory, University College London, 5 University St., London, WC1E 6JF, United Kingdom, or at s.janes@ucl.ac.uk.

N Engl J Med 2021;385:1207-18.
DOI: 10.1056/NEJMra1912719

CME at NEJM.org

CAUSES

Asbestos exposure is the most common cause of malignant mesothelioma. Arguably the most notable case series that supports this relationship was reported in the 1960s, in what was then the north west of Cape Province in South Africa, where 33 cases were examined, all involving exposure to clinically significant levels of asbestos.[5] Asbestos is an excellent insulating material that is strong, cheap, fire-resistant, and durable. Although its use has been banned in many countries as a result of its link to malignant mesothelioma, mining continues, with export for use in developing economies, which is expected to perpetuate the global incidence of exposure (Fig. 1).[6-8]

Mesothelioma has a latency period of 20 to 50 years.[9] Despite the identification of asbestos as an indisputable precipitant of mesothelioma, the precise pathogenetic mechanisms behind the development of the disease remain unclear. Contributing factors such as the persistence of mineral fibers (particularly asbestos) and chronic inflammation, supported by mouse models, have been extensively

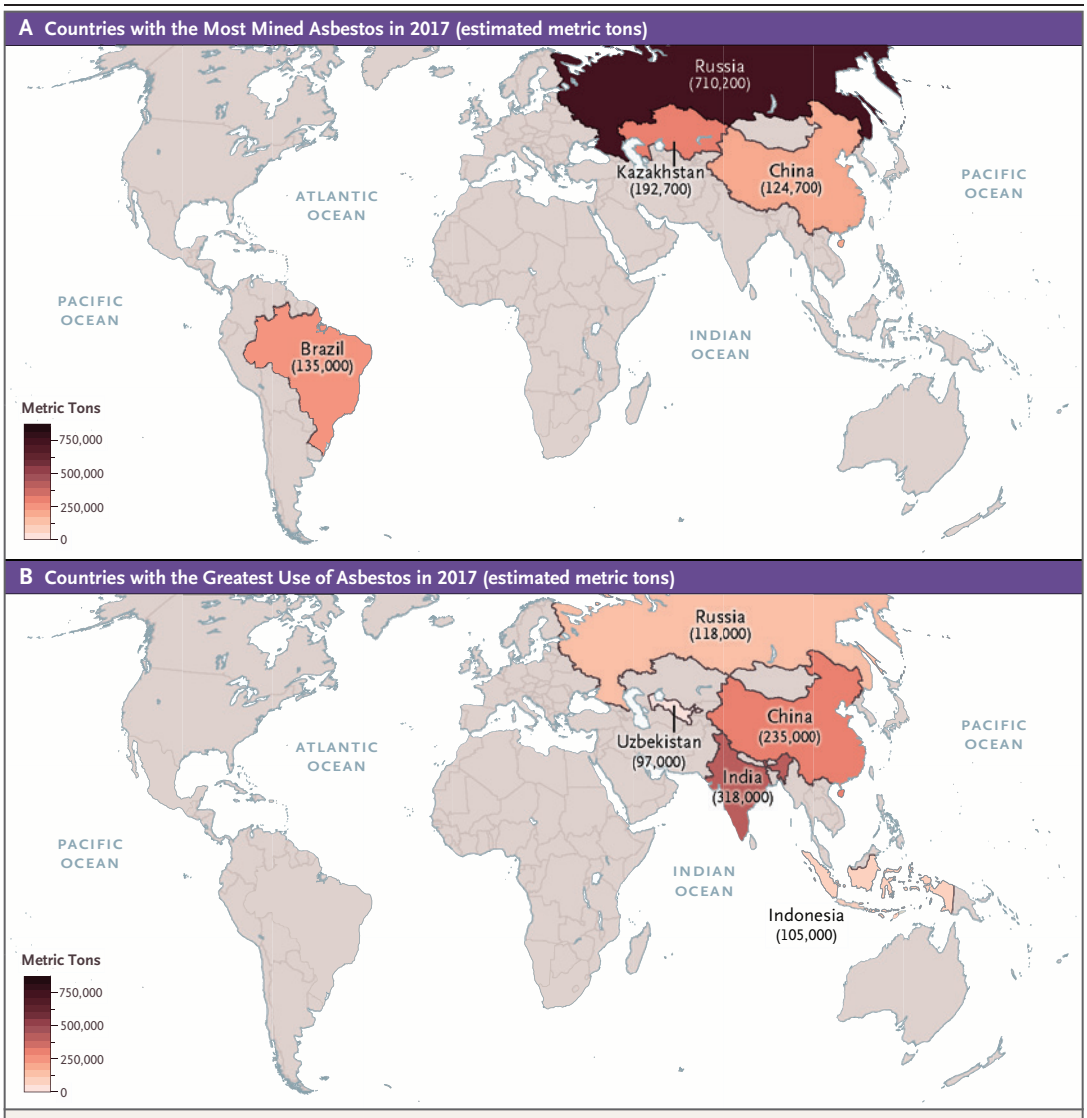


Figure 1. Global Asbestos Mining and Use of Asbestos.

The maps are based on data from the U.S. Geological Survey. In 2017, the countries with the most mined asbestos (measured in metric tons) were Russia, Kazakhstan, Brazil, and China (Panel A), and the countries with the greatest use of asbestos (measured in metric tons) were India, China, Russia, Indonesia, and Uzbekistan (Panel B).

reviewed elsewhere.[10,11] Analysis of the mutational signature of malignant pleural mesothelioma, an emerging research tool for detecting genomic footprints of damage, reveals mutational changes induced by reactive oxygen species. Asbestos-specific signatures have not yet been identified.[12,13]

In more than 10% of patients with malignant mesothelioma, germline variants have been reported.[14] Mutations in the gene encoding BRCA1-associated protein 1 (*BAP1*) have been shown to accelerate asbestos-induced mesothelioma in mice[15] and are associated with a syndrome consisting of familial cancers in humans, including malignant mesothelioma and uveal melanoma.[16] Other deleterious germline variants in DNA repair genes, such as *PALB2* and *BRCA1/2*, also accelerate the development of asbestos-induced mesothelioma in preclinical models and humans.[17]

HISTOPATHOLOGICAL AND MOLECULAR HETEROGENEITY

Three distinct histologic subtypes of pleural mesothelioma phenotypes have traditionally been recognized: epithelioid mesothelioma (accounting for 50 to 60% of cases), which is associated with the most favorable prognosis; sarcomatoid mesothelioma (10% of cases), which is highly invasive and drug-resistant; and biphasic mesothelioma (30 to 40% of cases), which is a mosaic of the other two subtypes. Recent insights reveal an epithelioid–sarcomatoid continuum rather than discrete subclasses, which correlates strongly with molecular markers of epithelial mesenchymal transition.[18] The interpatient heterogeneity of the disease has almost certainly hindered clinical trial design and results. The classic histologic subgrouping has also been challenged by the use of deep learning. Examination of both tumor heterogeneity and surrounding tumor stroma has revealed prognostic histopathological features such as inflammation, cellular diversity, and vacuolization within the stroma.[19]

Comprehensive genomic and transcriptomic sequencing of mesothelioma has revealed extensive genomic heterogeneity among patients, which probably underpins the failure of one-size-fits-all approaches to therapy. The mutational landscape of mesothelioma is dominated by the inactivation of tumor suppressor genes, which include *BAP1*, *CDKN2A*, *NF2*, and *SETD2*.[20,21]

The protracted interval between initial exposure and diagnosis suggests that mesothelioma, like breast cancer and cervical cancer, has a premalignant state. Indeed, loss of function of *BAP1* has been shown to be associated with a carcinoma in situ–like phenotype in the pleura and peritoneum, a potentially important finding for our understanding of the pathogenesis of mesothelioma, which is likely to influence future work exploring preventive therapeutic interventions.[22]

CLINICAL PRESENTATION

Most patients with malignant pleural mesothelioma present late in the course of the disease, as a result of asymptomatic early development, a sequela of the indolent biologic features of the disorder. The most common presenting symptoms at diagnosis include breathlessness caused by a pleural effusion or tumor encasement of the lung and the more sinister chest pain due to direct invasion into the chest wall or mediastinum. Fatigue, anorexia, weight loss, sweats, and malaise may also be present and become more frequent as the disease progresses.[23]

DIAGNOSIS

Contrast-enhanced computed tomography (CT) of the chest and upper abdomen is recommended as the initial method of investigation.[24] Other imaging techniques can be used to support the CT findings. Positron-emission tomography (PET) with CT has been shown to add diagnostic value when the CT results are uncertain regarding a malignant process, although PET-CT findings should be interpreted with caution, since areas of high metabolic activity may represent infection or inflammation.[25] Magnetic resonance imaging can provide greater soft-tissue definition, offering more detailed information on isolated foci of disease, chest-wall invasion, or infiltration into surrounding structures.[26] When the diagnosis remains uncertain, the more invasive techniques of mediastinoscopy, laparoscopy, endobronchial ultrasonography, and endoscopic ultrasonography are occasionally used if a positive result would influence management.[27] Several studies of serum-based and pleural fluid–based biomarkers, such as soluble mesothelin-related peptide and osteopontin, offer little evidence for their use in diagnosing malignant pleural mesothelioma or monitoring treatment effects.[24]

Diagnostic imaging guides histopathological confirmation of malignant pleural mesothelioma. Pleural biopsy is often the preferred diagnostic method; however, examination of pleural fluid is also an acceptable diagnostic method for epithelioid pleural mesothelioma. Diagnostic sensitivity varies widely, and higher rates of successful diagnoses are found in centers specializing in cytologic assessment of pleural effusion.[28,29]

Ancillary studies are key in supporting a histopathological diagnosis of malignant pleural mesothelioma. Immunohistochemical panels for biopsy specimens or cytologically derived cell blocks usually include at least two mesothelial markers (e.g., calretinin, cytokeratin 5/6, Wilms' tumor 1 antigen, or D2-40), which should be

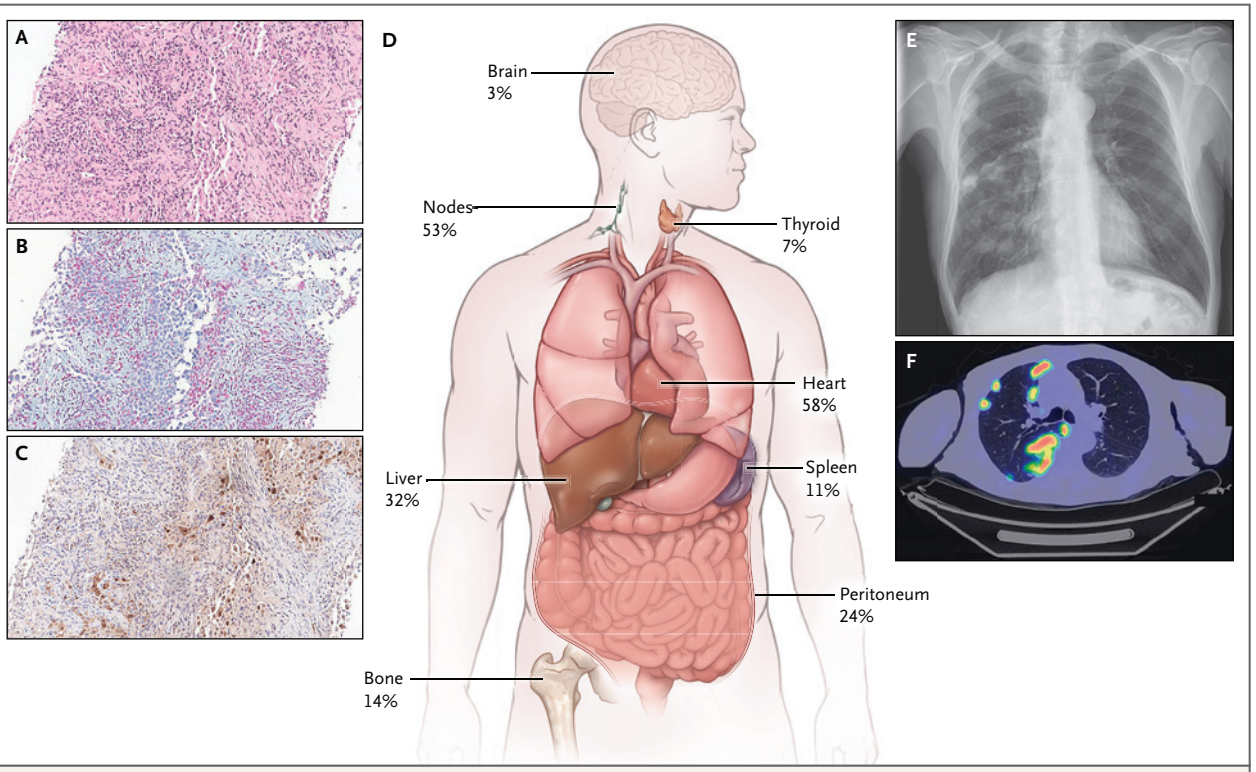


Figure 2. Histopathological Features, Anatomical Distribution, and Radiologic Detection of Malignant Mesothelioma.

Panel A shows sheets of epithelioid tumor cells with focal necrosis in lung tissue (hematoxylin and eosin). Panel B shows loss of BAP1 nuclear staining in tumor cells, with BAP1 staining retained in alveolar and inflammatory cells (pink). Panel C shows calretinin (tumor cells with both cytoplasmic and nuclear staining [brown]). Panel D shows some sites of extrapleural dissemination of disease from malignant pleural mesothelioma on the basis of postmortem studies.[33] Nodes represent those in hilar, mediastinal, and abdominal locations, and the heart represents pericardium and myocardium. Other sites of extrapleural disease, such as the kidney (9%) and adrenal glands (10%), are not shown. Panel E shows pleural mesothelioma detected on a chest radiograph, and Panel F shows detection on positron-emission tomography–CT.

positive, and two adenocarcinoma markers (e.g., thyroid transcription factor 1, carcinoembryonic antigen, or Ber-EP4), which should be negative. However, the sensitivity and specificity of these markers for the sarcomatoid subtype are poor. The absence of nuclear expression of BAP1 has emerged as an important diagnostic tool. Nuclear expression has been shown to be lost in up to 60% of cases, most often in the epithelioid subtype.[30] In addition to BAP1, p16INK4A and methylthioadenosine phosphorylase, which are frequently deleted on chromosome 9p21.3, have been shown to be helpful as markers of a malignant process[24,31,32] (Fig. 2).

STAGING

Patients usually present with localized pleural disease on radiologic assessment. However, postmortem studies often show widespread, unsuspected dissemination. These findings suggest that metastases may be missed at the initial presentation, potentially leading to understaging.[33]

Several iterations of staging systems for malignant pleural mesothelioma have been proposed; the most recent is the eighth edition of the International Association for the Study of Lung Cancer tumor–node–metastasis (TNM) grading system.[34] Its role in quantifying disease by measuring pleural infiltration, lymph-node involvement, and distant metastatic sites allows for identification of patients who would be candidates for participation in clinical trials of surgery and radiotherapy. Patients known to have advanced disease often proceed to conventional systemic treatment or clinical trial enrollment. The recognized discrepancy between radiologic and postmortem findings complicates

the development of predictive prognostic tools.[33,35] Furthermore, other key prognostic variables, such as histologic subtype, are not considered in TNM staging, making prognosis difficult to establish with the use of this approach alone.

CURRENT TREATMENT LANDSCAPE

Treatment of malignant pleural mesothelioma is guided by staging, histologic subtype, and the patient's functional status. Patients with inoperable disease are assessed for the use of systemic treatment or active symptom control. The latter approach, which focuses on symptom management, is a fundamental aspect of patient care. However, delivering it early rather than when required was not shown to improve quality-of-life measures in the United Kingdom–based RESPECT-Meso randomized trial.[36]

PLEURAL FLUID MANAGEMENT

Patients frequently present with pleural effusions requiring drainage for both symptom relief and diagnostics. Temporary catheterization of the pleural space to draw off fluid is usually accompanied by talc administration. The success rate with this approach is similar to the rates with indwelling catheterization and surgical procedures such as partial pleurectomy and pleurectomy–decortication, although the surgical procedures have higher complication rates and require a longer hospital stay.[37,38]

SURGERY

Surgical resection for mesothelioma is always incomplete and should be considered palliative (Fig. 3). Median survival after the most radical form of surgery, extrapleural pneumonectomy, is 18 months, with a 5-year survival rate of 14%.[39] It remains unclear whether cytoreductive surgery prolongs median survival for patients with malignant pleural mesothelioma. Studies to date have not provided a clear measure of the magnitude of benefit (vs. risk). Geographic inconsistencies in the recommendation of treatment for patients with early-stage disease are well recognized. To measure the efficacy of surgery for mesothelioma, appropriately controlled and well-powered randomized trials are essential.

The only reported data from a randomized trial directly comparing surgery with no surgery are from the United Kingdom–based Mesothelioma and Radical Surgery (MARS) feasibility study.[40] Patients treated with standard-of-care, platinum-based chemotherapy were randomly assigned, if their cancer had not progressed, to either surgery and radiotherapy or observation alone. Not only was the median overall survival shorter in the surgical group (14.4 months vs. 19.5 months), but morbidity was significantly higher. Although the adjusted hazard ratio for extrapleural pneumonectomy as compared with no extrapleural pneumonectomy was very high (2.75, $P=0.02$), it has been argued that this negative study was not sufficiently well powered. The considerable dropout rate from the originally screened 301 patients to 50 patients was problematic. Of the 24 patients randomly assigned to surgery, only 16 (67%) proceeded with surgery and only half of those received postoperative radiotherapy. Furthermore, patients who did not undergo surgery had more favorable biologic disease than those who did undergo surgery, which may have influenced the final outcome.[24,32] In response to these findings, MARS2, a randomized phase 3 trial, is assessing whether extended pleurectomy–decortication (a less radical procedure than extrapleural pneumonectomy) (Fig. 3) plus chemotherapy prolongs survival, as compared with chemotherapy alone.[41] If the results of this trial are negative, the role of surgery in such patients will be seriously undermined.

RADIOTHERAPY

Randomized, controlled evaluation of radiotherapy has, to date, not shown any improvement in associated survival. Although conducted only as a phase 2 investigation, SAKK 17/04 is probably the most important study to highlight. Patients treated with neoadjuvant chemotherapy and extrapleural pneumonectomy in whom macroscopic clearance of disease was achieved were randomly assigned to either high-dose radiotherapy or surveillance. The trial failed to meet its primary end point of locoregional relapse-free survival; however, this outcome was marred by slow enrollment of patients undergoing extrapleural pneumonectomy and by poor macroscopic clearance, with only a third of the originally recruited patients randomly assigned to either hemithoracic radiotherapy or observation.[42] The individual benefit of radiotherapy is challenging to ascertain in a trimodal approach in which both neoadjuvant chemotherapy and radi-

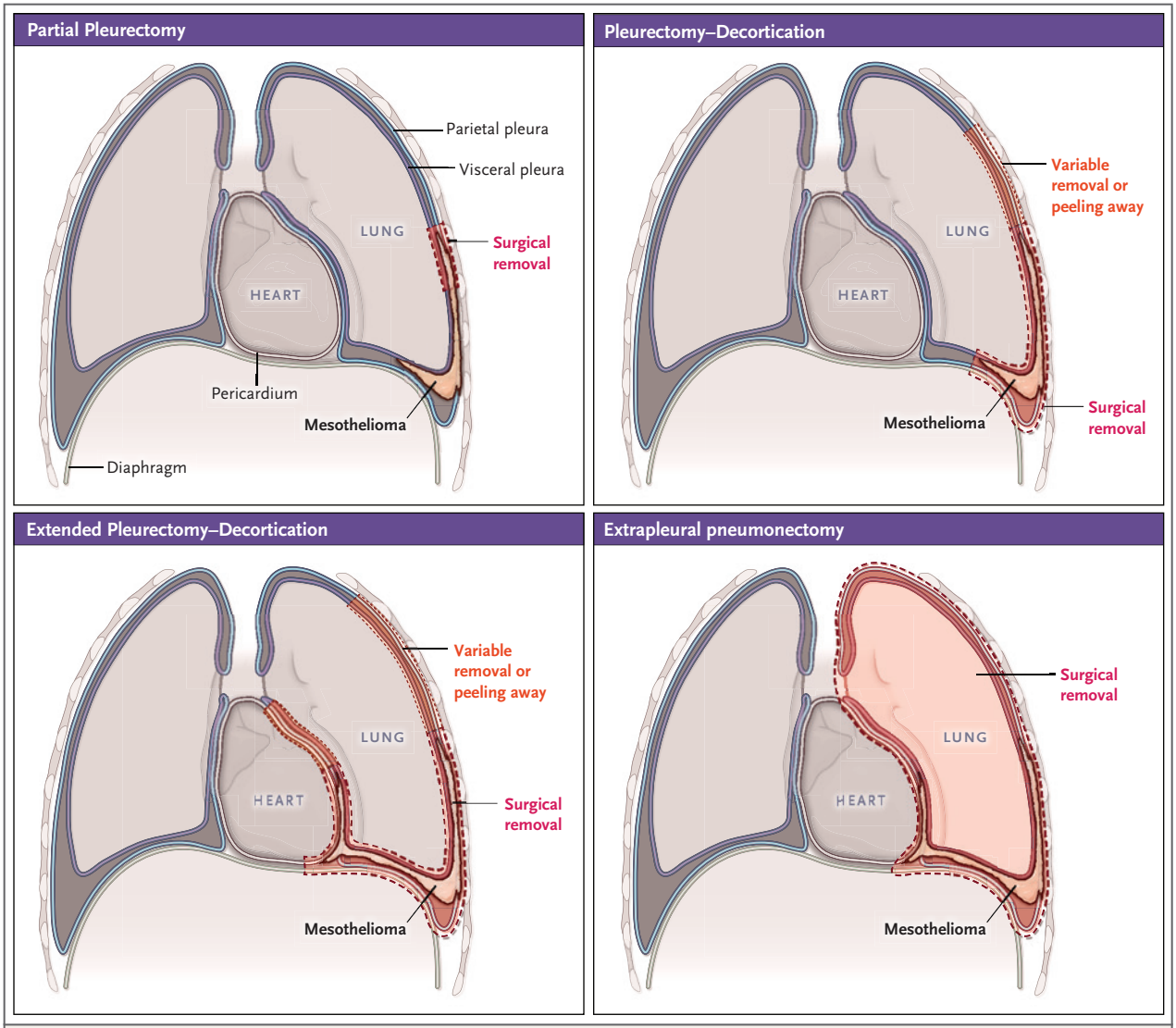


Figure 3. Surgical Approaches to the Treatment of Malignant Pleural Mesothelioma.

Partial pleurectomy entails partial removal of malignant pleural mesothelioma and effusion management. With pleurectomy–decortication, the affected pleura is removed, as is any visible tumor. Extended pleurectomy–decortication consists of pleurectomy–decortication plus removal of the pericardium and hemidiaphragm. Extrapleural pneumonectomy entails removal of the lung, pleura, pericardium, and hemidiaphragm, with the goal of macroscopic clearance of disease.

cal surgery remain under scrutiny. Other approaches, such as intensity-modulated radiotherapy and proton therapy, may reduce off-target damage. Intensity-modulated radiotherapy is being explored in a phase 3 clinical trial.[43,44]

Radiotherapy used as a prophylactic intervention to prevent chest-wall invasion after the use of diagnostic or therapeutic procedures has been widely abandoned because of negative results from two randomized, open-label phase 3 studies, Prophylactic Irradiation of Tracts (PIT)[45] and Surgical and Large-Bore Procedures in Malignant Pleural Mesothelioma and Radiotherapy trial (SMART).[46] Efforts to ascertain the role of radiotherapy in pain control are under way in the randomized SYSTEMS-2 study.[47]

TUMOR-TREATING FIELDS

The noninvasive delivery of alternating electric fields to mesothelioma tumors in combination

with platinum-based chemotherapy has shown activity in a single-group, phase 2 study of epithelioid disease. As a result, this combination has been approved by the Food and Drug Administration (FDA) as part of its Humanitarian Device Exemption program. The approval surprised many researchers, given the lack of randomization. Randomized data would provide valuable insight into the relative magnitude of the clinical benefit, toxicity, and cost-effectiveness.[48]

SYSTEMIC THERAPY

Until very recently, clinically meaningful advances in systemic treatment for advanced malignant pleural mesothelioma have been lacking. In the United States, over half of the patients never receive chemotherapy, largely because of older age, poor performance status, associated coexisting conditions, and ultimately, personal preference.[49] The EMPHACIS study defined the first standard-of-care front-line treatment, which received FDA approval in 2004. The study showed a significant increase in median overall survival from 9.3 months with cisplatin alone to 12.1 months with cisplatin combined with pemetrexed.[50] Raltitrexed combined with cisplatin was also shown to be superior to cisplatin alone, supporting the use of antifolate treatment for malignant pleural mesothelioma.[51]

The Mesothelioma Avastin plus Pemetrexed-Cisplatin Study (MAPS) showed that standard-of-care chemotherapy combined with bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor, improved survival (18.8 months, vs. 16.1 months with chemotherapy alone). Despite the small survival advantage, this treatment regimen was never filed for a license. Doubt remains regarding the value of adding bevacizumab to chemotherapy for patients with malignant pleural mesothelioma, especially in view of the increased adverse-event profile associated with combination therapy despite improvements in certain quality-of-life measures such as pain.[52] A subsequent study of the multitargeted antiangiogenic kinase inhibitor nintedanib had negative results.[53]

Immune checkpoint inhibition leading to tumor-suppressive T-cell activation has transformed systemic therapy for multiple solid tumors. Two important studies will imminently alter the way mesothelioma is treated in the future. On the basis of promising activity in patients with relapsed disease,[54] combination immunotherapy with nivolumab and ipilimumab, targeting the immune checkpoints programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte antigen 4, respectively, has shown superiority as a front-line treatment as compared with standard-of-care chemotherapy (survival, 18.1 months vs. 14.1 months), particularly in patients with nonepithelioid mesothelioma. This prespecified interim analysis led to FDA approval of the combination immunotherapy in 2020, the only systemic treatment for malignant pleural mesothelioma to be approved by the FDA since 2004.[55] The adverse-event profile of this regimen in older, more frail patients, as compared with the trial participants, will be observed with interest. Nivolumab alone is also the first drug to be associated with a significant improvement in overall survival among patients with relapsed mesothelioma. The recently reported Checkpoint Blockade for Inhibition of Relapsed Mesothelioma (CONFIRM) study showed a 3-month improvement in overall survival with nivolumab as compared with placebo.[56] The benefit was independent of programmed death ligand 1 (PD-L1) expression, a predictive marker of the response to anti–PD-1 therapy in patients with other tumors.[57] Survival updates are eagerly awaited, with the hope that a subgroup of patients will have durable responses, as observed in patients with other immunotherapy-sensitive tumors (Table 1).

No phase 3 trial of maintenance therapy (long-term treatment to delay a relapse after induction chemotherapy) has shown an improvement in overall survival.[58-60] Treatment with gemcitabine chemotherapy immediately after front-line chemotherapy (called switch maintenance) offers promise and warrants exploration in a phase 3 study.[61]

When durable responses have been observed with front-line chemotherapy, a rechallenge of platinum–pemetrexed can be useful in some patients.[62] Vinorelbine, another cytotoxic chemotherapeutic agent, has shown some activity,[63] and the results of a randomized trial should be available in 2021 (ClinicalTrials.gov number, NCT02139904).[64]

THE FUTURE LANDSCAPE

CHEMOIMMUNOTHERAPY

Combining an immune checkpoint inhibitor with chemotherapy has proved to be synergistic and

Table 1. Notable Phase 3 Clinical Trials of Immunotherapeutic Approaches to Malignant Pleural Mesothelioma (MPM).

Study Name	Description	ClinicalTrials.gov Number	Study Treatments	Status
Dendritic Cell Immunotherapy for Mesothelioma (DENIM)	Randomized, open-label phase 2–3 study of dendritic cells loaded with allogeneic tumor-cell lysate as maintenance treatment (MesoPher [Amphera]) after chemotherapy	NCT03610360	MesoPher plus best supportive care vs. best supportive care	Active but not recruiting
Pembrolizumab Immunotherapy versus Standard Chemotherapy for Advanced Pre-treated Malignant Pleural Mesothelioma (PROMISE-meso)	Multicenter, randomized phase 3 trial comparing pembrolizumab with standard chemotherapy for advanced, pretreated MPM	NCT02991482	Pembrolizumab vs. standard chemotherapy	Negative
Checkpoint Blockade for Inhibition of Relapsed Mesothelioma (CONFIRM)	Phase 3, double-blind, placebo-controlled trial to evaluate the efficacy of nivolumab in relapsed MPM	NCT03063450	Nivolumab vs. placebo	Positive
Pembrolizumab in Patients with Advanced Malignant Pleural Mesothelioma	Phase 2–3 randomized study of pembrolizumab in patients with advanced MPM	NCT02784171	Pemetrexed–cisplatin vs. pemetrexed–cisplatin plus pembrolizumab vs. pembrolizumab (phase 2 only)	Active but not recruiting
CheckMate 743*	Phase 3, randomized, open label trial of nivolumab plus ipilimumab vs. pemetrexed and platinum as first-line therapy in unresectable MPM	NCT02899299	Nivolumab plus ipilimumab vs. pemetrexed and platinum	Positive at prespecified interim analysis
INFINITE*	Phase 3, open-label, randomized, parallel group study to evaluate the efficacy and safety of intrapleural administration of adenovirus-delivered interferon alfa-2b (rAd-IFN) in combination with celecoxib and gemcitabine in patients with MPM	NCT03710876	rAd-IFN plus oral celecoxib and gemcitabine, then maintenance gemcitabine vs. oral celecoxib and gemcitabine, then maintenance gemcitabine	Active but not recruiting
Bevacizumab and Atezolizumab in Malignant Pleural Mesothelioma (BEAT-meso)	Multicenter, randomized phase 3 trial comparing atezolizumab plus bevacizumab and standard chemotherapy with bevacizumab and standard chemotherapy as first-line treatment for advanced MPM	NCT03762018	Bevacizumab plus chemotherapy vs. atezolizumab plus bevacizumab plus chemotherapy	Recruiting
Durvalumab with Chemotherapy as First Line Treatment in Advanced Pleural Mesothelioma (DREAM3R)	Phase 3 randomized trial of durvalumab with chemotherapy as first-line treatment in advanced pleural mesothelioma	NCT04334759	Durvalumab plus chemotherapy, then maintenance durvalumab vs. chemotherapy, then observation	Recruiting

* CheckMate 743 is the Study of Nivolumab Combined with Ipilimumab versus Pemetrexed and Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma Patients, and INFINITE is Efficacy and Safety of rAd-IFN Administered with Celecoxib and Gemcitabine in Patients with Malignant Pleural Mesothelioma.

is now a standard of care for patients with non–small-cell lung cancer.[65] Accordingly, for patients with mesothelioma, randomized trials targeting either PD-1 or its natural ligand, PD-L1, in combination with chemotherapy have shown potential or are ongoing (NCT02784171).[66] On the basis of the results from MAPS[67] and the premise that antiangiogenic agents encourage the differentiation and activity of immune cells, the addition of the PD-L1 inhibitor atezolizumab to pemetrexed–carboplatin and bevacizumab is being evaluated in a randomized phase 3 trial, Bevacizumab and

Atezolizumab in Malignant Pleural Mesothelioma (BEAT-meso; NCT03762018).

Delivery of adenovirus-mediated interferon alfa-2b is currently being evaluated in the phase 3 INFINITE study, on the basis of encouraging phase 2 data showing a disease control rate of 88%.[68] Previously treated patients are randomly assigned to receive either intrapleural adenovirus treatment followed by treatment with celecoxib and then gemcitabine or celecoxib and gemcitabine alone, until disease progression or termination of treatment because of toxic effects (NCT03710876). Studies such as these rely on the presence of accumulated pleural fluid to allow for placement of an indwelling pleural catheter, meaning that if the treatment is successful, not all patients are likely to benefit. Local treatment to the pleura has long been a goal for clinicians because of concerns regarding tumor penetration with the use of intravenous treatment.

CELLULAR THERAPY

Manipulating the immune system not only offers the opportunity for longer-term disease control than with chemotherapy but also is associated with fewer toxic effects. Innovative ways of modifying the behavior of the immune system have been explored. Genetically engineered T cells called chimeric antigen receptor T (CAR-T) cells have been designed to target mesothelin, an antigen predominantly but not exclusively seen on mesothelioma cells. A phase 1 clinical trial exploring intrapleural delivery of these CAR-T cells, combined with an immune checkpoint inhibitor, in 19 patients with pleural mesothelioma showed a disease control rate of almost 60%, an exciting finding in such an early-phase study.[69]

MOLECULARLY STRATIFIED THERAPY

Currently, no predictive biomarkers are in routine use for identifying patients who are likely to benefit from treatment for mesothelioma. However, a greater understanding of the biology of malignant mesothelioma has revealed molecular targets, opening up the possibility of an individualized approach (Fig. 4).

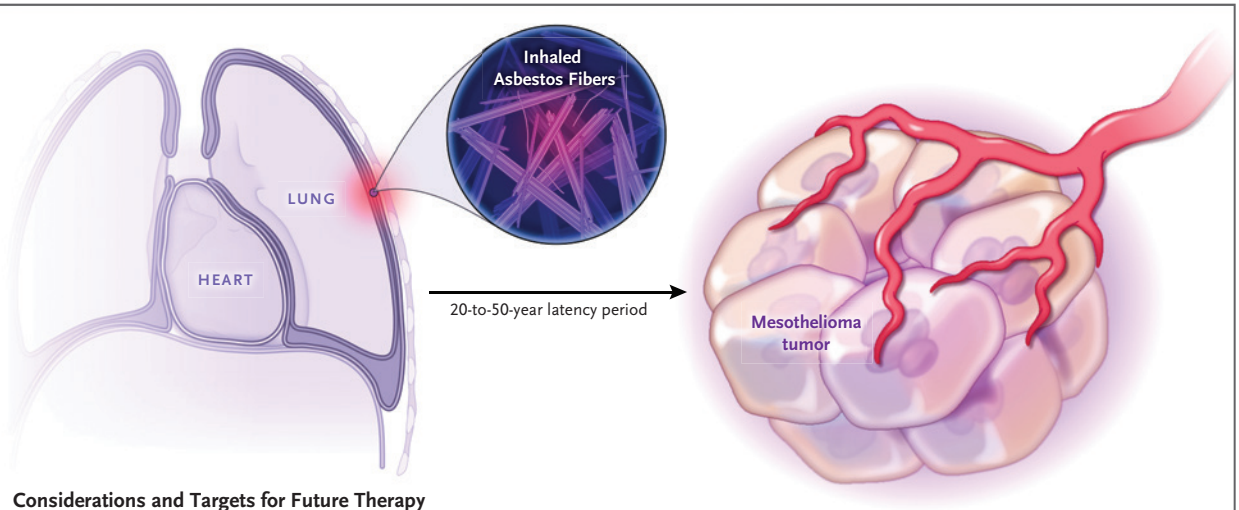
Epigenetic silencing of the enzyme argininosuccinate synthetase 1 (ASS1) represents the first target to undergo molecularly stratified phase 3 evaluation in patients with mesothelioma. Loss of ASS1 leads to a reliance on exogenous arginine for viability[70] and exposes a therapeutically exploitable vulnerability with the use of arginine deprivation. Treatment with pegylated arginine deiminase (ADI-PEG 20), which leads to a decrease in arginine, has shown efficacy in a randomized phase 2 trial[71] and can be safely combined with chemotherapy.[72] Since ASS1 loss is most common in patients with nonepithelioid mesothelioma, a placebo-controlled phase 3 trial evaluating standard chemotherapy with or without ADI-PEG 20 in this subgroup of patients is ongoing (NCT02709512).

Tumor-suppressor gene losses, which predominate in mesothelioma, may confer sensitivity to new small molecules, providing an opportunity for drug development. BAP1 inactivation leads to up-regulation of the oncogenic polycomb repressive complex 2. One of its subunits, enhancer of zeste homolog 2 (EZH2), has been shown to lead to cancer progression.[73] A phase 2 multicenter clinical trial of the EZH2 inhibitor tazemetostat in BAP1-inactivated malignant mesothelioma met its primary end point of disease control at 12 weeks (51% of patients).[74]

Master protocols (trials designed to assess multiple hypotheses) provide a platform that directly addresses interpatient heterogeneity through individualized therapy. Molecular stratification of mesothelioma as a basis for individualizing therapy is now possible. The Mesothelioma Stratified Therapy (MiST) trial is the first rolling, multigroup, phase 2 umbrella study that has been designed to rapidly evaluate new treatments coupled to "multi-omic" interrogation and to identify predictive biomarkers of an exceptional response.[75] In one MiST group (patients with BAP1/BRCA1-deficient mesothelioma who received rucaparib), the disease control rate was 58% at 12 weeks and 23% at 24 weeks.[76] The MiST protocol is hypothesis-generating, with the aim of accelerating and guiding future stratified, randomized trials.

CONCLUSIONS

Progress in improving survival for patients with mesothelioma has been slow. This can be partly explained by a lack of randomized trials, particularly for surgical treatment. Extensive interpatient heterogeneity represents another major barrier, warranting stratified therapy. To accelerate advances in the field, we must embrace rational, well-controlled investigations, as well



Considerations and Targets for Future Therapy

Phenotypic Histologic Subtypes	
Epithelioid (50–60% of cases)	
Biphasic (30–40% of cases)	
Sarcomatoid (10% of cases)	

Current and Future Systemic Approaches
Chemotherapy
Antibody-drug conjugates
Immune checkpoint inhibition (PD-1 or PD-L1 inhibition)
Ferroptosis inducers
Cellular therapy (CAR-T cells targeting mesothelin)
Angiogenesis inhibition

Genomic or Epigenomic Landscape	
Mutation	**Therapeutic Targets**
BAP1	EZH2; PARP
CDKN2A	p16
NF2	FAK; YAP-TEAD; mTOR and PI3K
ASS1	Arginine

Figure 4. Future Therapeutic Approaches to Malignant Pleural Mesothelioma.
Future treatment decisions may be based on morphologic differences, the immune microenvironment of the tumor, and the genomic or epigenomic landscape that promotes a biomarker-based strategy.

as individualized approaches. Master protocols could accelerate the discovery of new, effective treatments. Continued increases in the incidence of malignant pleural mesothelioma in developing countries warrant ongoing scientific and clinical pursuit of new, effective, and affordable treatments.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Daisuke Nonaka and James Spicer, at Guy's Hospital, London, for providing the histopathological and radiologic images, respectively; Dr. Julia Ruston, at Lungs for Living Research Centre, for help with an earlier version of the artwork; and Dr. Kate Gowers, at Lungs for Living Research Centre, for assistance with the preparation of an earlier version of the manuscript.

REFERENCES

1. Milano MT, Zhang H. Malignant pleural mesothelioma: a population-based study of survival. J Thorac Oncol 2010;5:1841-8.
2. Carbone M, Emri S, Dogan AU, et al. A mesothelioma epidemic in Cappadocia: scientific developments and unexpected social outcomes. Nat Rev Cancer 2007;7:147-54.
3. Mazurek JM, Syamlal G, Wood JM, Hendricks SA, Weston A. Malignant mesothelioma mortality — United States, 1999-2015. MMWR Morb Mortal Wkly Rep 2017;66:214-8.
4. Mesothelioma statistics for Great Britain, 2021. Health and Safety Executive. July 2021 (https://www.hse.gov.uk/statistics/causdis/mesothelioma/mesothelioma.pdf).
5. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Br J Ind Med 1960;17:260-71.
6. Odgerel CO, Takahashi K, Sorahan T, et al. Estimation of the global burden of mesothelioma deaths from incomplete national mortality data. Occup Environ Med 2017;74:851-8.
7. Allen LP, Baez J, Stern MEC, Takahashi K, George F. Trends and the economic effect of asbestos bans and decline in asbestos consumption and production worldwide. Int J Environ Res Public Health 2018;15:531.
8. Chen T, Sun XM, Wu L. High time for complete ban on asbestos use in developing countries. JAMA Oncol 2019;5:779-80.
9. Sekido Y. Molecular pathogenesis of malignant mesothelioma. Carcinogenesis 2013;34:1413-9.
10. Røe OD, Stella GM. Malignant pleural mesothelioma: history, controversy and

future of a manmade epidemic. Eur Respir Rev 2015;24:115-31.
11. Carbone M, Ly BH, Dodson RF, et al. Malignant mesothelioma: facts, myths, and hypotheses. J Cell Physiol 2012;227:44-58.
12. Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. Nat Genet 2016;48:407-16.
13. Hmeljak J, Sanchez-Vega F, Hoadley KA, et al. Integrative molecular characterization of malignant pleural mesothelioma. Cancer Discov 2018;8:1548-65.
14. Panou V, Gadiraju M, Wolin A, et al. Frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. J Clin Oncol 2018;36:2863-71.
15. Xu J, Kadariya Y, Cheung M, et al. Germline mutation of Bap1 accelerates development of asbestos-induced malignant mesothelioma. Cancer Res 2014;74:4388-97.
16. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet 2011;43:1022-5.
17. Panou V, Rϕe OD. Inherited genetic mutations and polymorphisms in malignant mesothelioma: a comprehensive review. Int J Mol Sci 2020;21:4327.
18. Blum Y, Meiller C, Quetel L, et al. Dissecting heterogeneity in malignant pleural mesothelioma through histo-molecular gradients for clinical applications. Nat Commun 2019;10:1333.
19. Courtiol P, Maussion C, Moarii M, et al. Deep learning-based classification of mesothelioma improves prediction of patient outcome. Nat Med 2019;25:1519-25.
20. Yoshikawa Y, Sato A, Tsujimura T, et al. Frequent inactivation of the BAP1 gene in epithelioid-type malignant mesothelioma. Cancer Sci 2012;103:868-74.
21. Sato T, Sekido Y. NF2/merlin inactivation and potential therapeutic targets in mesothelioma. Int J Mol Sci 2018;19:988.
22. Churg A, Galateau-Salle F, Roden AC, et al. Malignant mesothelioma in situ: morphologic features and clinical outcome. Mod Pathol 2020;33:297-302.
23. Parker C, Neville E. Lung cancer * 8: management of malignant mesothelioma. Thorax 2003;58:809-13.
24. Woolhouse I, Bishop L, Darlison L, et al. British Thoracic Society guideline for the investigation and management of malignant pleural mesothelioma. Thorax 2018;73:Suppl 1:i1-i30.
25. Basu S, Saboury B, Torigian DA, Alavi A. Current evidence base of FDG-PET/CT imaging in the clinical management of malignant pleural mesothelioma: emerging significance of image segmentation and global disease assessment. Mol Imaging Biol 2011;13:801-11.
26. Bibby AC, Tsim S, Kanellakis N, et al. Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment. Eur Respir Rev 2016;25:472-86.
27. Wald O, Groth SS, Burt BM, Sugarbaker DJ. Role of thoracoscopy, mediastinoscopy and laparoscopy in the diagnosis and staging of malignant pleural mesothelioma. J Vis Surg 2016;2:129.
28. Hjerpe A, Ascoli V, Bedrossian CW, et al. Guidelines for the cytopathologic diagnosis of epithelioid and mixed-type malignant mesothelioma: complementary statement from the International Mesothelioma Interest Group, also endorsed by the International Academy of Cytology and the Papanicolaou Society of Cytopathology. Acta Cytol 2015;59:2-16.
29. Henderson DW, Reid G, Kao SC, van Zandwijk N, Klebe S. Challenges and controversies in the diagnosis of mesothelioma. 1. Cytology-only diagnosis, biopsies, immunohistochemistry, discrimination between mesothelioma and reactive mesothelial hyperplasia, and biomarkers. J Clin Pathol 2013;66:847-53.
30. Carbone M, Yang H, Pass HI, Krausz T, Testa JR, Gaudino G. BAP1 and cancer. Nat Rev Cancer 2013;13:153-9.
31. Nicholson AG, Sauter JL, Nowak AK, et al. EURACAN/IASLC proposals for updating the histologic classification of pleural mesothelioma: towards a more multidisciplinary approach. J Thorac Oncol 2020;15:29-49.
32. Kindler HL, Ismaila N, Armato SG III, et al. Treatment of malignant pleural mesothelioma: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2018;36:1343-73.
33. Finn RS, Brims FJH, Gandhi A, et al. Postmortem findings of malignant pleural mesothelioma: a two-center study of 318 patients. Chest 2012;142:1267-73.
34. Rusch VW, Chansky K, Kindler HL, et al. The IASLC Mesothelioma Staging Project: proposals for the M descriptors and for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for mesothelioma. J Thorac Oncol 2016;11:2112-9.
35. Brims FJ, Meniawy TM, Duffus I, et al. A novel clinical prediction model for prognosis in malignant pleural mesothelioma using decision tree analysis. J Thorac Oncol 2016;11:573-82.
36. Brims F, Gunatilake S, Lawrie I, et al. Early specialist palliative care on quality of life for malignant pleural mesothelioma: a randomised controlled trial. Thorax 2019;74:354-61.
37. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA 2012;307:2383-9.
38. Rintoul RC, Ritchie AJ, Edwards JG, et al. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. Lancet 2014;384:1118-27.
39. Sugarbaker DJ, Richards WG, Bueno R. Extrapleural pneumonectomy in the treatment of epithelioid malignant pleural mesothelioma: novel prognostic implications of combined N1 and N2 nodal involvement based on experience in 529 patients. Ann Surg 2014;260:577-80.
40. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol 2011;12:763-72.
41. Lim E, Darlison L, Edwards J, et al. Mesothelioma and Radical Surgery 2 (MARS 2): protocol for a multicentre randomised trial comparing (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma. BMJ Open 2020;10(9):e038892.
42. Stahel RA, Riesterer O, Xyrafas A, et al. Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemithoracic radiotherapy (SAKK 17/04): a randomised, international, multicentre phase 2 trial. Lancet Oncol 2015;16:1651-8.
43. Gomez DR, Rimner A, Simone CB II, et al. The use of radiation therapy for the treatment of malignant pleural mesothelioma: expert opinion from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation. J Thorac Oncol 2019;14:1172-83.
44. Rimner AHC, Zauderer M, Yorke ED, et al. A phase III randomized trial of pleurectomy/decortication plus chemotherapy with or without adjuvant hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) for malignant pleural mesothelioma (MPM) (NRG-LU006). Int J Radiat Oncol 2020;108:E928-E929.
45. Bayman N, Appel W, Ashcroft L, et al. Prophylactic irradiation of tracts in patients with malignant pleural mesothelioma: an open-label, multicenter, phase III randomized trial. J Clin Oncol 2019;37:1200-8.
46. Clive AO, Taylor H, Dobson L, et al. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial. Lancet Oncol 2016;17:1094-104.
47. Ashton M, O'Rourke N, Macleod N, et al. SYSTEMS-2: a randomised phase II study of radiotherapy dose escalation for pain control in malignant pleural meso-

thelioma. Clin Transl Radiat Oncol 2017;8:45-9.
48. Ceresoli GL, Aerts JG, Dziadziuszko R, et al. Tumour treating fields in combination with pemetrexed and cisplatin or carboplatin as first-line treatment for unresectable malignant pleural mesothelioma (STELLAR): a multicentre, single-arm phase 2 trial. Lancet Oncol 2019;20:1702-9.
49. Beebe-Dimmer JL, Fryzek JP, Yee CL, et al. Mesothelioma in the United States: a Surveillance, Epidemiology, and End Results (SEER)-Medicare investigation of treatment patterns and overall survival. Clin Epidemiol 2016;8:743-50.
50. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636-44.
51. van Meerbeeck JP, Gaafar R, Manegold C, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. J Clin Oncol 2005;23:6881-9.
52. Eberst G, Anota A, Scherpereel A, et al. Health-related quality of life impact from adding bevacizumab to cisplatin-pemetrexed in malignant pleural mesothelioma in the MAPS IFCT-GFPC-0701 phase III trial. Clin Cancer Res 2019;25:5759-65.
53. Scagliotti GV, Gaafar R, Nowak AK, et al. Nintedanib in combination with pemetrexed and cisplatin for chemotherapy-naive patients with advanced malignant pleural mesothelioma (LUME-Meso): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet Respir Med 2019;7:569-80.
54. Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. Lancet Oncol 2019;20:239-53.
55. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet 2021;397:375-86.
56. Fennell D, Ottensmeier C, Califano R, et al. Nivolumab versus placebo in relapsed malignant mesothelioma: preliminary results from the CONFIRM phase 3 trial. Presented at International Association for the Study of Lung Cancer (IASLC) 2020 World Conference on Lung Cancer (WCLC), held virtually, January 28–31, 2021. abstract PS02.11.
57. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823-33.
58. Kindler H, Scherpereel A, Calabro L, et al. Tremelimumab as second- or third-line treatment of unresectable malignant mesothelioma (MM): results from the global, double-blind, placebo-controlled DETERMINE study. J Clin Oncol 2016;34:8502.
59. Popat S, Curioni-Fontecedro A, Dafni U, et al. A multicentre randomised phase III trial comparing pembrolizumab versus single-agent chemotherapy for advanced pre-treated malignant pleural mesothelioma: the European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial. Ann Oncol 2020;31:1734-45.
60. Fennell DA, Baas P, Taylor P, et al. Maintenance defactinib versus placebo after first-line chemotherapy in patients with merlin-stratified pleural mesothelioma: COMMAND — a double-blind, randomized, phase II study. J Clin Oncol 2019;37:790-8.
61. de Gooijer CJ, van der Noort V, Stigt JA, et al. Switch-maintenance gemcitabine after first-line chemotherapy in patients with malignant mesothelioma (NVALT19): an investigator-initiated, randomised, open-label, phase 2 trial. Lancet Respir Med 2021;9:585-92.
62. Ceresoli GL, Zucali PA, De Vincenzo F, et al. Retreatment with pemetrexed-based chemotherapy in patients with malignant pleural mesothelioma. Lung Cancer 2011;72:73-7.
63. Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. Lung Cancer 2009;63:94-7.
64. Fennell DA, Casbard A, Nixon L, Lester J, Griffiths G. Vinorelbine in Mesothelioma (VIM): a randomised phase II trial of oral vinorelbine as second-line therapy for patients with malignant pleural mesothelioma (MPM) expressing BRCA1 — a study in progress. Ann Oncol 2012;23:IX498.
65. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078-92.
66. Nowak A, Kok P, Lesterhuis W, et al. DREAM — a phase 2 trial of durvalumab with first line chemotherapy in mesothelioma: final result. J Thorac Oncol 2018;13:S338-S339.
67. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet 2016;387:1405-14.
68. Sterman DH, Alley E, Stevenson JP, et al. Pilot and feasibility trial evaluating immuno-gene therapy of malignant mesothelioma using intrapleural delivery of adenovirus-IFNα combined with chemotherapy. Clin Cancer Res 2016;22:3791-800.
69. Adusumilli PS, Zauderer MG, Rusch VW, et al. A phase I clinical trial of malignant pleural disease treated with regionally delivered autologous mesothelin-targeted CAR T cells: safety and efficacy. In: Proceedings of the American Association for Cancer Research Annual Meeting March 29–April 3, 2019. Atlanta: American Association for Cancer Research, 2019:CT036. abstract.
70. Szlosarek PW, Klabatsa A, Pallaska A, et al. In vivo loss of expression of argininosuccinate synthetase in malignant pleural mesothelioma is a biomarker for susceptibility to arginine depletion. Clin Cancer Res 2006;12:7126-31.
71. Szlosarek PW, Steele JP, Nolan L, et al. Arginine deprivation with pegylated arginine deiminase in patients with argininosuccinate synthetase 1-deficient malignant pleural mesothelioma: a randomized clinical trial. JAMA Oncol 2017;3:58-66.
72. Beddowes E, Spicer J, Chan PY, et al. Phase 1 dose-escalation study of pegylated arginine deiminase, cisplatin, and pemetrexed in patients with argininosuccinate synthetase 1-deficient thoracic cancers. J Clin Oncol 2017;35:1778-85.
73. LaFave LM, Béguelin W, Koche R, et al. Loss of BAP1 function leads to EZH2-dependent transformation. Nat Med 2015;21:1344-9.
74. Zauderer MG, Szlosarek P, Le Moulec S, et al. Phase 2, multicenter study of the EZH2 inhibitor tazemetostat as monotherapy in adults with relapsed or refractory (R/R) malignant mesothelioma (MM) with BAP1 inactivation. J Clin Oncol 2018;36:8515.
75. Fennell D, Hudka M, Darlison L, et al. P2.06-02 Mesothelioma Stratified Therapy (MiST): a phase IIA umbrella trial for accelerating the development of precision medicines. J Thorac Oncol 2019;14:S755-S756.
76. Fennell DA, King A, Mohammed S, et al. Rucaparib in patients with BAP1-deficient or BRCA1-deficient mesothelioma (MiST1): an open-label, single-arm, phase 2a clinical trial. Lancet Respir Med 2021;9:593-600.