Contemporary management of mesothelioma

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Shareable abstract (@ERSpublications)
Contemporary mesothelioma management needs multidisciplinary input. First-line treatment may include immunotherapy or chemotherapy. There is no proven standard of care for early-stage disease. Trials should be prioritised especially in relapsed disease. https://bit.ly/4dLkZk4

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Abstract

Pleural mesothelioma (PM) is an aggressive asbestos-associated thoracic malignancy with a median survival of 12–18 months. Due to continued asbestos use in many nations, global incidence is rising. Causes due to non-occupational, environmental exposure are also rising in many countries despite utilisation bans. For many years, platinum–pemetrexed chemotherapy was the solitary licensed therapy, but first-line combination immune checkpoint blockade has recently demonstrated improved outcomes, with both regimes tested in predominantly late-stage cohorts. In the second-line setting, single-agent nivolumab has been shown to extend survival and is now available for routine use in some regions, while second-line chemotherapy has no proven role and opportunities for clinical trials should be maximised in relapsed disease. Surgery for "technically resectable" disease has been offered for decades in many expert centres, but the recent results from the phase III MARS2 trial have challenged this approach. There remains no robustly proven standard of care for early-stage PM. The clinical trial landscape for PM is complex and increasingly diverse, making further development of specialist PM multidisciplinary teams an important priority in all countries. The observation of improving outcomes in centres that have adopted this service model emphasises the importance of high-quality diagnostics and equitable access to therapies and trials. Novel therapies targeting a range of aberrations are being evaluated; however, a better understanding of the molecular drivers and their associated vulnerabilities is required to identify and prioritise treatment targets.

Educational aims

- Understand the current treatment options available for patients with pleural mesothelioma including surgery, systemic therapies and radiotherapy.
- Understand the importance of subtype and stage in current treatment stratification with an awareness of the associated limitations and the necessity for specialist input.
- Be aware of the growing portfolio of pleural mesothelioma studies and the urgent need for an evidence-based standard of care for patients with early-stage disease.

Introduction

Pleural mesothelioma (PM) is an invasive thoracic malignancy causally linked to prior asbestos exposure in most patients [1, 2]. The association between asbestos and PM was first established by Wagner in South African miners in the 1960s, but exposure in most European patients reflects involvement in heavy industries or construction or environmental contamination [3]. Import and utilisation bans were implemented across Western Europe in the late 1990s or early 2000s, but many environments remain contaminated by asbestos-containing building materials. Outside Europe, asbestos is still used in many nations, including the USA, while others, including Russia, India, China and Indonesia, continue to mine asbestos and/or manufacture asbestos products [4]. The World Health Organization (WHO) recently estimated that 125 million people are exposed to asbestos annually and predicted that the current global incidence of 30 000 cases per year will exceed 50 000 per year by 2040 [5, 6]. With a typical latency of

30–50 years between asbestos exposure and disease manifestation, PM is typically a disease of older individuals [1, 5]. However, this reflects historic occupational exposure patterns, and as environmental exposures increase, including exposure in school children, this age distribution may change.

In this review, we provide an overview of current PM management, focusing on those therapies that are commonly available in routine care. We begin with a strategic overview regarding the organisation of care and the key factors involved in treatment planning, including symptom control. This is followed by data pertaining to surgical therapy, systemic therapies, and radiotherapy. We conclude with perspectives on emerging approaches and also direct the reader to comprehensive treatment guidelines published by European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS)/European Association for Cardio-Thoracic Surgery (EACTS)/European Society for Radiotherapy and Oncology (ESTRO) [2] and European Society for Medical Oncology (ESMO) [1].

Treatment planning

Organisation of care and specialist multidisciplinary teams

PM is an uncommon cancer and disease incidence will vary considerably by region, based on patterns of asbestos exposure. In the UK, this results in areas of extremely high incidence (*e.g.* in the West of Scotland) in relative proximity to areas of low incidence (*e.g.* the North of Scotland). This patchy distribution makes it difficult to ensure equitable high-quality care for all patients, since specialist diagnostic and staging tools are of critical importance. One solution to this is network working, where equitable access to evidence-based methods is explicitly prioritised, including appropriate imaging, use of thoracoscopy for tissue acquisition, and access to expert pathology and radiology review as part of management planning. This model has been successfully deployed in the Scottish Mesothelioma Network, which has recently reported improving outcomes, including survival, in >600 patients managed over 6 years [7]. Population data from Scotland also contradict previous retrospective series regarding stage distribution. In Scotland, where all patients are managed (and staged) by a specialist multidisciplinary team (sMDT), >50% of new cases had stage I disease. Similarly, in a prospective multicentre observational study across 25 UK sites, where all cases were reviewed by PM sMDTs, the incidence of stage I disease was 34% [8]. These figures are considerably higher than the 5.3–17.4% rate of stage I disease reported in earlier retrospective series, where staging data was frequently missing and data were extracted from lung cancer sMDTs, with variable familiarity with PM staging criteria [9, 10].

Radiological staging

Radiological staging is currently based on the eighth TNM (tumour, node, metastasis) edition (figure 1) [2, 11], although this is due to be updated during 2024. Accurate staging requires venous phase contrast-enhanced computed tomography (CT) of the thorax and upper abdomen as a minimum. Additional staging, using integrated positron emission tomography (PET)/CT ± magnetic resonance imaging (MRI) should be performed if radical surgery is being considered [1, 2]. This reflects the well-documented limitations of CT for detection of pleural, nodal and metastatic disease, with the latter two being of particular importance prior to surgery [2, 12]. A comprehensive review of pre-surgical staging methods has recently been reported elsewhere [13].

Unusually for a solid cancer, the current T-stage descriptors for PM make no reference to tumour size, being based instead on the extent of invasion into adjacent structures (see figure 2) [11]. This reflects a historical bias in previous staging series towards surgical selection criteria and the challenges involved in quantitative measurement of a complex, rind-shaped tumour like PM. This morphology violates mathematical assumptions regarding a roughly spherical tumour, which underpin commonly used relationships between simple unidimensional measurements and true volume. Direct volumetric measurement is the obvious solution to this, but previous studies report high inter-rater inconsistencies when human readers perform this task [14]. In the near future, it is likely that artificial intelligence (AI) volumetry tools will solve this problem and the first fully automated convolutional neural network for this purpose [15] is currently being validated as part of the Cancer Research UK-funded PREDICT-Meso International Accelerator Network. In the imminent next iteration of the staging system, it is expected that tumour thickness measurements will be introduced as a surrogate for true volume, pending routine deployment of AI solutions.

Pathology

Histological classification

The recently updated WHO histological classification defines three PM subtypes: epithelioid, sarcomatoid and biphasic. Biphasic disease is defined arbitrarily by a >10% sarcomatoid element in predominantly epithelioid disease [16]. Histological subtyping is highly prognostic with median overall survival (mOS) varying from 16.5 to 8.8 months in epithelioid and sarcomatoid cohorts, with biphasic mOS intermediate

T	Description	N0	N1	N2	M1
T1	Tumour limited to the ipsilateral pleura (parietal±visceral/mediastinal/diaphragmatic)	1A	2	3B	4
T2	Tumour involving all ipsilateral pleural surfaces with either: • Involvement of the diaphragmatic muscle • Involvement of the pulmonary parenchyma	1B	2	3B	4
T3	Describes locally advanced, *technically resectable* tumour. Tumour involving all ipsilateral pleural surfaces with any of the following: • Extension to the endothoracic fascia • Extension to the mediastinal fat • Non-transmural involvement of the pericardium • A solitary, focus of tumour extending into the chest wall	1B	3A	3B	4
T4	Describes locally advanced, *technically unresectable* tumour. Tumour involving all the ipsilateral pleural surfaces with any of the following: • Involvement of the contralateral pleura • Tumour extension to the mediastinal organs • Tumour extension to the spine • Transmural involvement of the pericardium and/or myocardium • Diffuse or multifocal tumour in the chest wall±associated rib destruction	3B	3B	3B	4

FIGURE 1 An overview of the eighth edition of the Pleural Mesothelioma Staging System, produced by the International Assocation for the Study of Lung Cancer (IASLC) and International Mesothelioma Interest Group (iMig). T: tumour; N: node. Information from [2, 11].

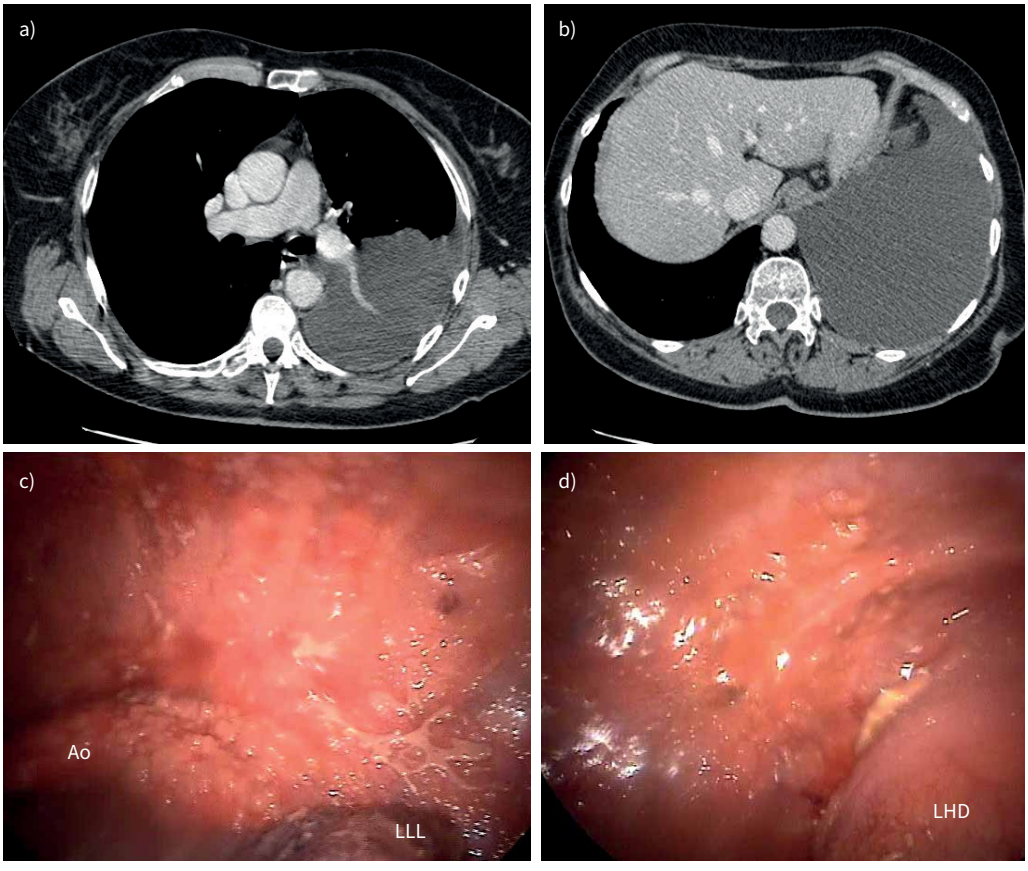

FIGURE 2 a, b) Axial computed tomography images of a patient with stage I pleural mesothelioma. These demonstrate a large pleural effusion, but no obvious areas of pleural thickening. c, d) Local anaesthetic thoracoscopy images recorded in the same patient demonstrating widespread parietal pleural tumour after complete evacuation of the large pleural effusion. Note the descending thoracic aorta (Ao) also covered by tumour, the deflated left lower lobe (LLL) and the left hemidiaphragm (LHD). Reproduced and modified from [58] with permission.

between these two cohorts [2, 16]. The current WHO guidelines also recommend grading of epithelioid cases for additional prognostic information [16], and expert pathologist involvement *via* a sMDT is critical for delivery of these tasks. Histological classification is also critical for treatment planning, given the divergent outcomes in non-epithelioid subtypes treated using immune checkpoint inhibitors (ICIs) (better outcomes) and surgery (worse outcomes) [2, 17]. However, this task is complicated by both intratumour heterogeneity and spatial heterogeneity, with multiple tumours commonly visible at thoracoscopy across the vast pleural surface area, even in early-stage disease (see figure 2) [17]. Thoracoscopy is therefore the gold standard biopsy method, not only permitting full thickness biopsies and the highest diagnostic sensitivity, but also multiregion sampling, which offers the maximum opportunity to detect any non-epithelioid component. Chirieac *et al.* [18] confirm that the accuracy of histological classification increases with the number of tissue blocks examined. Therefore, the general recommendation is 4–10 thoracoscopic biopsies per patient, representative of macroscopically abnormal pleura. This will not be feasible for all patients, as technical limitations and patient tolerance must be considered.

Molecular features

Salient molecular features of PM include a low mutational burden and a genomic landscape dominated by tumour suppressor loss, with few oncogenic drivers [19, 20]. PM tumours are also highly stromal, comprising a complex tumour microenvironment infiltrated by macrophages, lymphocytes and cancer-associated fibroblasts [21]. Increasing appreciation of this complexity reveals the inadequacy of current histological subtyping methods. Unsupervised clustering of RNA sequencing (RNASeq) data demonstrates four, not three, distinct tumour subtypes: epithelioid, sarcomatoid, biphasic-E and biphasic-S [19]. Using this method, 68% of histologically classified epithelioid tumours were molecularly classified as biphasic-E, assigning a significantly worst prognosis. Using multi-omic data (DNA sequencing, RNASeq and methylation profiling), Mangiante *et al.* [22] recently concluded that current histological subtyping accounts for only 6% of observed inter-patient molecular heterogeneity. In this study, different features (ploidy, morphology, immune infiltration and CpG island methylation) explained considerably more variation (33%), suggesting a more prominent future clinical role for molecular stratification [22]. Nevertheless, at present, the only tissue feature used in treatment planning remains basic histological subtype.

Symptom control

Symptom burden is often high in PM and active symptom management needs to accompany diagnostic work-up. A comprehensive review is beyond the scope of this article, but management of dyspnoea, pain and constitutional symptoms should be prioritised.

Dyspnoea

Dyspnoea due to pleural effusion is the most common presenting feature of PM. In a large, multicentre prospective study of PM diagnostics, Tsim *et al.* [8] reported that 91% of 152 PM patients had effusion at presentation, of which 71% were symptomatic. Options for definitive management of effusion in PM include indwelling pleural catheter (IPC) insertion and talc pleurodesis (TP). Previous high-quality phase III trials demonstrate the broad equivalence of these techniques, as defined by breathlessness scores; however, the adverse event profiles differ for each intervention [23–25]. By virtue of their placement in outpatient settings, IPCs are associated with reduced initial time in hospital [25]. IPCs are also effective in palliating breathlessness in non-expansile lung (NEL), which is frequently occult and is the commonest reason for TP failure. However, IPCs are also associated with a higher burden of subsequent healthcare contacts [26] and an enduring risk of infection. TP is typically effective in ∼75% of malignant pleural effusions, with no proven benefit from talc poudrage over ward-based talc slurry [27]. However, some studies report reduced TP efficacy in PM [28, 29], which may reflect higher tumour volumes and/or a higher frequency of NEL (in up to a third of cases) [30].

The goal of definitive pleural management should be improved overall quality of life (QoL), of which breathlessness is only one component. The OPTIMUM trial is the only head-to-head trial of IPC *versus* TP that used QoL as a primary end-point, reporting improved QoL in both arms and no significant difference between the arms [31]. This highlights the importance of patient-centred and highly individualised decision making. Mitchell *et al.* [32] recently reported that alternative strategies were not always discussed with patients treated with IPCs, and outcomes post-insertion did not always meet expectations, highlighting the need for a comprehensive consent process. It should also be noted that although TP and IPC placement can both be performed during diagnostic thoracoscopy, efficiencies gained by this combined approach should be balanced against the risk of false negative sampling. An early pleurodesis may have important adverse consequences if further biopsies cannot be retrieved or if opportunities for intrapleural trials are removed (*e.g.* following TP). Effusion drainage, without immediate definitive management, is therefore reasonable until treatment planning is complete.

Pain

Chest wall pain is common in PM and may reflect direct tumour infiltration, a high-pressure pleural effusion or side-effects from pleural investigations or management [1]. In addition to routine analgesic regimens, combining paracetamol, nonsteroidal anti-inflammatories and opioids, neuropathic agents may be of benefit. In localised pain, palliative radiotherapy should be considered (see the section titled "Radiotherapy") [1, 2]. Patients with more diffuse hemithoracic pain may benefit from cervical cordotomy, but a recent systematic review (nine studies, 160 patients) highlighted the low quality of evidence for the technique [33]. Cordotomy should therefore be considered by a PM sMDT involving palliative/pain medicine.

Constitutional symptoms

Constitutional symptoms are common, including anorexia, weight loss and overt cachexia. Nutritional supplementation with/without low-dose steroids may be effective in maintaining caloric intake, but the latter should be used with caution, especially if treatment with immunotherapy may be feasible. The EXTRA-Meso (EXercise TheRApy in Mesothelioma Study) feasibility trial is currently evaluating whether a future phase III trial of an exercise intervention would be possible as a potential means of maintaining muscle mass, function and QoL [34].

Treatment modalities

Surgery

The evidence base supporting surgical therapies in PM is limited, with no phase III study reporting superior outcomes from any intervention in any stage of disease. Despite this, surgical interventions have for many years been offered in many specialist centres. These include extrapleural pneumonectomy (EPP), which involves removal of the diseased pleura, in addition to the lung, pericardium and hemidiaphragm, and lung-sparing surgery, properly defined as pleurectomy/decortication (P/D), which involves a parietal and visceral pleurectomy with the intention of removing all visible tumour [1, 2]. Extended P/D (EPD) additionally includes resection of the diaphragm and/or pericardium if these surfaces are affected [1, 2]. In contrast, partial pleurectomy (also referred to as partial P/D) always leaves visible tumour behind and is generally performed as a combined diagnostic and palliative procedure [29, 35]. The MesoVATS trial reported no survival advantage in patients allocated to partial P/D (hazard ratio for death at 1 year 1.04 (95% CI 0.76–1.42); p=0.81) relative to a those treated by simple TP [35]. Partial P/D was also associated with a longer hospital stay, more complications and increased cost [35].

With regard to more aggressive surgical options, complete tumour resection with microscopically negative margins is not feasible in PM due to the unique shape of the primary tumour and its intimate relationship with surrounding critical structures [36, 37]. The objective of "radical" surgery is therefore macroscopic complete resection (MCR), with adjuvant or neo-adjuvant systemic therapy and/or radiotherapy generally considered necessary [1, 2]. MCR can be achieved by EPP or EPD [36, 38], but the former is now rarely used due to increased perioperative mortality and morbidity in multiple series [37–40], a meta-analysis of 2903 patients [41] and the MARS feasibility trial [39]. The ESMO and ERS/ESTS/EACTS/ESTRO guidelines both advocate cautious use of MCR, suggesting it should only be considered in highly selected patients (*e.g.* those with epithelioid disease, no nodal involvement and minimal comorbidity) [1, 2]. This guidance reflects several phase II studies which reported favourable long-term outcomes following EPD [36]. However, these studies were systematically biased due to stringent selection criteria [37]. Both guidelines advocate that EPP should not be used, while the earlier British Thoracic Society guidelines advise that any attempt at MCR (including EPD) should only be offered in the context of a clinical trial [42]. The recently completed MARS2 phase III trial, which conference proceedings recently reported increased mortality and reduced QoL in patients treated by neoadjuvant chemotherapy, EPD with/without adjuvant chemotherapy compared with chemotherapy alone seems likely to further diminish enthusiasm for MCR in most centres. This trial has not been published in full at the time of writing.

Systemic therapy

First-line platinum–pemetrexed chemotherapy

The first standard of care for PM was defined in the EMPHACIS study, which reported superior overall survival (OS) in patients treated with cisplatin and the antifolate metabolite pemetrexed (Cis/Pem) compared with cisplatin monotherapy (median OS 12.1 *versus* 9.3 months; p=0.02), in patients fully supplemented with folic acid and vitamin B12 [43]. Based on outcomes from a large, expanded access programme reported by Santoro *et al.* [44], carboplatin/pemetrexed is accepted as offering similar efficacy to Cis/Pem with improved tolerability. Both regimens are typically administered for up to six cycles in the absence of progression or toxicity, with no current evidence to support the role of maintenance therapy [1, 2]. Notably, non-epithelioid PM is characterised by chemoresistance with inferior outcomes consistently reported [43, 45]. The EMPHACIS cohort primarily included advanced stage patients, with 78% in stage

III/IV, meaning there is limited evidence for use of Cis/Pem in stage I PM [43]. This is important given the frequency of stage I cases in cohorts staged through sMDTs (see the section titled "Organisation of care and specialist multidisciplinary teams").

First-line immune checkpoint inhibition

While ICIs have revolutionised the treatment of several solid tumours, outcomes in PM have been less dramatic, including negative initial trials using single agents (*e.g.* DETERMINE study [46]). In the first-line setting, CheckMate743 evaluated the combination of nivolumab, a programmed cell death protein 1 (PD-1) receptor blocker that restores anti-tumour T-cell function, and ipilimumab, a cytotoxic T-lymphocyte associated protein (CTLA-4) receptor blocker that induces *de novo* anti-tumour T-cell responses in 605 patients with unresectable PM [1, 47]. Patients were randomised (1:1) to nivolumab once every 2 weeks plus ipilimumab once every 6 weeks for up to 2 years or up to six cycles of Cis/Pem. The study demonstrated a significant OS survival benefit in the ipilimumab/nivolumab arm (median OS 18.1 (95% CI 16.8–21.4) *versus* 14.1 (95% CI 12.4–16.2) months; hazard ratio 0.74, p=0.002) [47], an effect that was driven by non-epithelioid cases (18.1 *versus* 8.8 months; hazard ratio 0.48 (95% CI 0.34–0.69)) [47]. However, the mOS in epithelioid and non-epithelioid cases was similar with the main difference between the arms being the markedly inferior effect of Cis/Pem in non-epithelioid cases. Peters *et al.* [48] recently reported 3-year survival outcomes from CheckMate743, including 23.2% (95% CI 18.4–28.2) in ipilimumab/nivolumab treated patients compared with 15.4% (95% CI 11.5–19.9) in Cis/Pem. Much like the EMPHACIS Cis/Pem trial, CheckMate743 also recruited predominantly advanced stage PM (89% in stage III/IV), meaning the evidence for ipilimumab/nivolumab in stage I PM is also limited [47].

Ipilimumab/nivolumab is clearly the new standard of care for fit patients with non-epithelioid PM. While the data also support use in epithelioid cases, Cis/Pem may still be appropriate in this setting, for example, if there are particular contraindications (*e.g.* inflammatory arthritis) or where a rapid treatment response is felt critical. In CheckMate743, progression on ipilimumab/nivolumab often occurred early [47] and treatment response to ICIs were generally slower. Moreover, grade 3–4 treatment-related adverse events (TRAEs) were numerically higher with ipilimumab/nivolumab (15%) than with chemotherapy (7%) [47], although TRAEs were also associated with particularly good survival outcomes. Nevertheless, the possibility of early progression and the significant side-effect profile of ipilimumab/nivolumab should be important considerations in treatment planning.

Second-line systemic therapy

The evidence base for second-line treatment of relapsed PM is limited and entry to clinical trials should be actively considered, depending on local availability [1]. Single-agent chemotherapy has not been associated with extended survival in phase III trials, with modest radiological response rates observed in phase II trials [45]. The phase III VIM trial recently reported improved progression-free survival (PFS) for vinorelbine compared with best supportive care, but without any significant OS benefit [49]. Similarly, Jassem *et al.* [50] recently compared the efficacy of pemetrexed monotherapy *versus* best supportive care in relapsed PM. In this trial only 18.7% of patients had a radiological response, again with no significant benefit to OS reported [50].

A number of second-line immune-targeted trials have been reported recently, although most by definition recruited patients treated with Cis/Pem, making deployment in an era of first-line ICIs potentially challenging [51]. Early phase II trials using single-agent PD-1 and PD-L1 inhibitors reported radiological response rates ranging from 8% to 29% [2, 51]. The phase II MAPS2 trial reported higher ORR rates using ipilimumab/nivolumab (28%) or nivolumab alone (19%), with median OS for these arms of 15.9 and 11.9 months, respectively [52]. Conversely, the phase III randomised controlled trial (RCT), PROMISE-Meso reported no OS benefit for pembrolizumab when compared with single-agent chemotherapy (either vinorelbine or gemcitabine), despite a superior response rate [53].

Scherpereel *et al*. [2] suggest that the apparent inconsistency observed in ICI trials in relapsed PM may reflect inadequate patient selection, resulting in random, unpredictable and potentially unbalanced allocation of patients with adverse biology between trial arms. The MAPS2 trial used a stratification factor of time to progression following first-line therapy and dichotomised outcomes at 3 months [52], which included three toxicity-related deaths following ipilimumab/nivolumab [52]. By this method, rapidly progressing patients (<3 months) had the shortest OS, which was comparable with the mOS reported for the pembrolizumab arm within PROMISE-Meso [52, 53]. This reiterates the heterogenous nature of PM and highlights the need for molecular stratification in future trials, since failure to do so may hamper the identification of clinical efficacy signals [52].

Despite these challenges important progress has been made in the second-line setting. This includes the recently reported phase III CONFIRM trial, which compared nivolumab monotherapy to placebo and demonstrated superior PFS and OS (PFS 3.0 *versus* 1.8 months; HR 0.67 (95% CI 0.53–0.85), p=0.0012; OS 10.2 *versus* 6.9 months; HR 0.69 (95% CI 0.52–0.91), p=0.009), leading to the licensing of this therapy in some regions for second-line use [54]. The phase II RAMES study also reported improved OS using single-agent chemotherapy in combination with ramucirumab, an anti-vascular endothelial growth factor receptor 2 antibody [55]. A UK-based multicentre RCT, NERO, has recently completed recruitment exploring the role of niraparib in relapsed PM, following the phase II MiST1 trial [56].

Radiotherapy

Radiotherapy is commonly used for palliation of localised pain associated with a targetable tumour mass on CT imaging. However, PM is relatively radioresistant, with historical symptomatic response rates varying from 0% to 69% in a 2014 systematic review [57, 58]. The highest quality evidence for palliative radiotherapy comes from the phase II SYSTEMS trial, which reported pain improvement in only 35% using 20 Gy in five fractions [59]. Since PM has a low α/β ratio, predicting better responses to dose-escalated hypofractionated regimes [60], the SYSTEMS trial was followed by the phase III RCT, SYSTEMS-2, which compared 36 Gy in six fractions to 20 Gy in five fractions [61]. Mature data from this trial are expected during 2024.

Prophylactic radiotherapy was traditionally offered in some regions for prevention of procedure-tract metastases (PTM) following pleural intervention. In 2016, the phase III SMART trial provided conclusive evidence that this strategy was not justified [62]. They reported no reduction in PTM incidence in 203 patients randomised equally between immediate (prophylactic) radiotherapy and deferred radiotherapy if a tract metastasis developed [62]. A similar result was subsequently observed in the multicentre phase III PIT trial [63].

Radical radiotherapy does not have an established role in PM [64–66] and current guidelines recommend use only in clinical trials [2]. Delivery of radical doses has historically been hampered by toxicity to the adjacent lung and a high incidence of radiation pneumonitis. Adjuvant radical dosing was evaluated in the SAKK 17/04 trial following EPP, but no difference was observed in locoregional recurrence [67], and accrual to the trial was slow and ultimately below target. Recent technical advances may lead to new radical radiotherapy opportunities, *e.g.* using intensity-modulated radiotherapy (IMRT) or proton beam therapy (PBT). The recent phase II IMPRINT trial reported grade 3 radiation pneumonitis in only two out of 27 (7%) using IMRT, prompting a subsequent phase III trial [68], while PBT is currently being tested in the phase III HIT-Meso trial.

Future therapeutic strategies

In a recent consensus statement, Scherpereel *et al.* [2] stressed the importance of increased preclinical research to develop therapeutic hypotheses tailored to PM biology. Key components of this research will be enhanced preclinical models and positioning of these against deeply phenotyped human cohorts, enabling suitable preclinical avatars for therapeutic drug screening and target-drug validation. PM research should also respond to data emerging from programmes such TRACERx, which have revealed the true complexity of late-stage cancer, prompting a shift towards early detection and intervention by major research funders [69, 70].

Chemotherapy–immunotherapy

The disappointing activity of chemotherapy in PM has prompted multiple combinatorial strategies, including chemotherapy–immunotherapy (chemo-IO). Drugs currently being evaluated include anti-PD-1 blockers (pembrolizumab, nivolumab), anti-PD-L1 blockers (durvalumab, atezolizumab) and anti-CTLA4 blockers (ipilimumab, tremelimumab) [2]. The phase II DREAM trial, which combined durvalumab with standard dose Cis/Pem, followed by durvalumab maintenance for up to 12 months in 31 patients, recently met its primary end-point [71, 72]. In a similar trial using the same combination, PrE0505, mOS was 21.1 months [72]. These data have prompted initiation of DREAM3R, a global phase III RCT. The recently published phase III RCT, IND227, randomised 440 patients (1:1) to Cis/Pem or Cis/Pem plus pembrolizumab, with carboplatin/pemetrexed permitted if cisplatin was contraindicated [73]. With a median follow-up of 16.2 months, OS was significantly, albeit modestly, improved in the chemo-IO arm (mOS 17.3 *versus* 16.1 months; hazard ratio 0.79 (95% CI 0.64–0.98), p=0.0324) [73]. However, as with ipilimumab/nivolumab in CheckMate743, grade 3–4 TRAEs were numerically higher in the pembrolizumab chemo-IO arm of IND227 (27% *versus* 15%) [73]. Two further phase III RCTS are also in progress at the time of writing: BEAT-Meso, which is evaluating the role of Cis/Pem/bevacizumab±atezolizumab, and eVOLVE-Meso, which is evaluating the effect of volrustomig (a combined PD-1/CTLA-4 blocker) in addition to carboplatin/pemetrexed.

Targeted therapy

The paucity of obviously druggable oncogenic drivers in PM predicts limited success from targeted therapies. This is reflected in negative prior phase II studies using the small-molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), erlotinib and gefitinib, and the focal adhesion kinase (FAK) inhibitor, defactinib [74–76]. However, the phase III MAPS trial reported that bevacizumab, a vascular endothelial growth factor (VEGF) monoclonal antibody, in combination with Cis/Pem was associated with a modest 2.7-month extension in mOS compared to Cis/Pem alone (hazard ratio 0.77 (95% CI 0.62–0.95); p=0.0167) [77]. Unfortunately, the triplet combination was associated with an increased risk of adverse events (71% of patients experiencing grade 3 or 4 events), particularly hypertension and thrombosis, meaning regulatory approval has not followed for this regime. The phase III LUME-Meso trial evaluated nintedanib, an oral multitargeted angiokinase inhibitor with activity across VEGF and fibroblast growth factor receptors, in combination with Cis/Pem [78]. However, the primary end-point (PFS) was not met in this trial (6.8 months (95% CI 6.1–7.0) *versus* 7.0 months (95% CI 6.7–7.2); hazard ratio 1.01 (95% CI 0.79–1.3), p=0.91) with more adverse events associated with nintedanib [78].

Future targeted therapy strategies may involve more precise biomarker-directed designs or combinatorial approaches focused on inducing synthetic lethality rather than oncogenic inhibition of tumour growth. The genomic landscape in PM is dominated by inactivation of tumour suppressor genes, notably neurofibromin 2 (NF2), cyclin-dependent kinase inhibitor 2A (CDKN2A) and BRCA1 associated protein 1 (BAP1) [19, 58, 79]. The central role of these genes has been corroborated in preclinical mouse models reported by Farahmand *et al.* [80], in which the presence of asbestos-induced pleural inflammation accelerates disease progression over tumour suppressor loss alone. In preclinical studies, inactivation of BAP1 has been associated with resultant upregulation of EZH2 which belongs to a group of epigenetic regulators that repress transcription and subsequently alter gene expression patterns [81]. LaFave *et al.* [81] recently demonstrated that conditional deletion of BAP1 and EZH2 *in vivo* evades the myeloid progenitor expansion induced by BAP1 loss alone, while cells lacking BAP1 appear sensitive to EZH2 pharmacological inhibition, offering a novel therapeutic strategy.

Grosso *et al.* [82] have recently reported attempts to target protein translation for therapeutic purposes. PM tumour cells have elevated global levels of mRNA translation, including a selective increase in translation of proteins involved in ribosome assembly and mitochondrial biogenesis, and these events could potentially accelerate tumour cell growth in the absence of standard proto-oncogenic drivers [82]. In their study, Grosso *et al.* [82] established that inhibition of this process by pharmacological targeting of mTORC1/2, impaired PM tumour cell growth in preclinical models, including an asbestos-induced mouse system. This approach was broadly cytostatic rather than cytotoxic, suggesting deployment in early stages of the disease, even as chemoprophylaxis in high-risk pre-invasive patients may be most effective.

Intrapleural therapies

Intrapleural therapy has the potential to maximise tumour dose to the tumour-bearing pleural surfaces, while minimising systemic toxicity. Historical phase I/II trials reported encouraging response rates to various immunomodulatory agents [83–85], almost exclusively recruiting early-stage patients to first-line trials [83–85]. Following licensing of Cis/Pem, intrapleural trial designs shifted to second-line and beyond, where patients commonly had complex and often pleurodesed pleural spaces, and outcomes in this setting were less impressive with few radiological responses [86, 87]. However, the limited data supporting licensed systemic anti-cancer therapy (SACT) regimes in early-stage PM has prompted reconsideration of expansion of intrapleural trials to serve these patients. Intrapleural treatment is supported by contrast CT and MRI studies which suggest that, unlike most solid tumours, PM is poorly vascularised, meaning intrapleural dosing may be superior to *i.v.* dosing, with observations from a recent intrapleural CAR T-cell trial demonstrating successful distribution *via* the intrapleural route [87]. However, future intrapleural trials will need to address a number of important challenges. Ideally, they will use first-line designs to minimise pleural access problems and careful staging to accurately select patients with disease confined to the pleura (broadly equivalent to T1N0M0). In that setting, intrapleural trials could be integrated as "window-of-opportunity" studies, with first-line SACT (licensed for later stage "unresectable" disease) available on progression. Other challenges will include drug deposition, since therapies may need to penetrate through dense fibrous stroma to reach tumour cells not on the surface, and management of the pleural macroenvironment, including septation and a tendency for auto-pleurodesis over time. In the UK, a multicentre, phase I/II trial of the mitochondrial PRX3 inhibitor RSO-021 (MITOPE; clinicaltrials.gov identifier: NCT05278975) is currently recruiting. This is one of the first examples of a new generation of targeted intrapleural therapeutics, with first-line recruitment an option in the protocol.

Other approaches

A broad range of additional strategies are currently being explored but detailed discussion is beyond the scope of this article. These include mesothelin-targeted therapies, CAR T-cells, oncolytic viruses and novel immunotherapy agents [2, 88].

Biomarkers

There is an urgent need to identify noninvasive biomarkers which can reliably predict outcomes and guide therapeutic direction. As stated earlier, PM subtyping has profound implications on prognosis and treatment planning with non-epithelioid PM typically displaying chemoresistance and a superior relative response to first-line ipilimumab/nivolumab (although in absolute terms, outcomes are similar in both subtypes). PD-L1 has proven an unreliable predictive biomarker for immunotherapy response. In the second-line setting, both CONFIRM and PROMISE-Meso reported no correlation between tumour PD-L1 expression and PFS or OS [53, 54]. In CheckMate743, OS outcomes were similar in ipilimumab/nivolumab treated patients with PD-L1 expression <1% *versus* ⩾1% [47, 89]. However, in this study survival was shorter in patients allocated to chemotherapy with PD-L1 expression >1%, prompting the hypothesis that this marker might help direct Cis/Pem *versus* ipilimumab/nivolumab decision making, particularly in epithelioid patients where outcomes are otherwise fairly similar [47, 89]. In a recent systematic review, Mansfield *et al.* [89] additionally suggested that the cut-offs used to define PD-L1 status (frequently focused around 1%) may increase heterogeneity in outcomes, with several studies reporting more consistent results using higher cut-offs. Numerous other factors, including tumour mutational burden are known to influence treatment response, meriting further study in future trials [21]. Inactivation of BAP1 has also been associated with a more inflammatory tumour microenvironment and tumours harbouring this common mutation may have more permissive immune landscape, favouring response to ICIs [21, 81].

Conclusion

For many years, platinum–pemetrexed chemotherapy was the standard first-line approach for PM with no second-line options and limited clinical trial opportunities. However, the therapeutic landscape has radically altered over recent years, with establishment of first-line ipilimumab/nivolumab as the standard of care for most patients with later stage, “unresectable” disease. Recent results from the phase III MARS2 trial of EPD in combination with neoadjuvant±adjuvant chemotherapy challenge the concept of “resectable” disease and development of new trials for patients with earlier stages of PM is urgently needed. In the second-line setting, single-agent nivolumab has been shown to extend survival and is now available for routine use in some countries. Second-line chemotherapy has no proven role and opportunities for clinical trials should be maximised in this setting. The clinical trial landscape for PM is complex and increasingly diverse, making further development of PM sMDTs an important priority for all services. The observation of improving outcomes in centres that have adopted this service model emphasises the importance of high-quality diagnostics services and equitable access to therapies and trials.

Key points

- sMDTs improve outcomes in PM and offer improved access to a growing portfolio of clinical trials.
- Recent results from the phase III MARS2 trial challenge the concept of “resectable” disease leaving no current standard of care for many early-stage PM patients.
- Ipilimumab/nivolumab has now been established in the first-line setting and should be considered standard practice for non-epithelioid PM.
- PM research should focus on early detection and intervention in line with recent paradigm shifts within Cancer Research UK.

Self-evaluation questions

1. What features define the optimum diagnostic pathway for suspected PM, including the most suitable imaging and biopsy tests and service configuration?
2. What is the role of expert pathology review in PM, including the impact of histological subtype and grade on prognosis and treatment planning?
3. What are the key factors involved in managing symptomatic pleural effusion in patients with PM?
4. Describe the standard of care systemic therapy options for first-line treatment of PM, assuming performance status 1 and factoring in the impact of histological subtype and radiological stage.
5. What is the role of surgical treatment in PM?

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Suggested answers

1. The optimum diagnostic pathway for PM will focus on rapid access to an actionable diagnosis reliant on accurate histological staging and subtype. A venous phase contrast-enhanced CT of the thorax and abdomen forms the basis of current staging with additional imaging in the form of PET/CT±MRI typically performed where radical surgery is considered. Thoracoscopy is the gold standard biopsy method offering the highest diagnostic sensitivity alongside opportunities for the multi-region sampling required for accurate histological subtyping. PM is an uncommon cancer with unique staging parameters and challenging histological assessment. Diagnosis *via* an sMDT has been shown to improve outcomes and should be accessed where available.
2. Expert pathology review is an important aspect of the sMDT. Histological subtype is a key determinant of prognosis with sarcomatoid cohorts demonstrating the worst mOS. Differentiating epithelioid from non-epithelioid disease is currently crucial to treatment stratification where non-epithelioid disease is typically chemoresistant and more responsive to ICIs. Within epithelioid cohorts, further description of morphological features including grade are prognostic and important considerations for the sMDT.
3. Definitive management of symptomatic pleural effusion will involve either IPC or TP. The key determinant will be patient preference following a comprehensive consent process, which should consider factors such as time in hospital, ongoing healthcare contact, success rate and adverse events. TP should not be offered in the presence of known non-expansile lung and typically reserved until a histological diagnosis is established. IPCs have an enduring risk of adverse events including infection in an often-immunocompromised cohort. Reported side-effects also include discomfort, difficulty sleeping and IPCs acting as a reminder of disease. IPCs may permit entry into a growing portfolio of intrapleural drug trials, whilst strategies including IPC-PLUS are available.
4. First-line immune checkpoint inhibition with ipilimumab/nivolumab should be considered the standard of care for patients with non-epithelioid PM. Ipilimumab/nivolumab should also be offered to patients with

epithelioid disease, however Cis/Pem is still appropriate in this setting, particularly where ipilimumab/nivolumab is contraindicated. There is a limited evidence base to support first line SACT in early-stage PM where patients have "technically resectable disease". In these patients, entry into clinical trials should be offered.

5. Radical surgery in the form of EPD has traditionally been offered as part of multimodality treatment for patients with "technically resectable" epithelioid PM. Following the results of MARS-2 (awaiting publication) enthusiasm for the role of surgery will diminish. In most centres surgery will now be offered only as part of a clinical trials following sMDT input. Surgery has no role in PM symptom control.