ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma

Arnaud Scherpereel[1,2], Isabelle Opitz[3], Thierry Berghmans[4], Ioannis Psallidas[5], Markus Glatzer[6], David Rigau[7], Philippe Astoul[8], Servet Bölükbas[9], Jeanette Boyd[10], Johan Coolen[11], Charlotte De Bondt[12], Dirk De Ruysscher[13], Valerie Durieux[14], Corinne Faivre-Finn[15], Dean Fennell[16], Francoise Galateau-Salle[17], Laurent Greillier[18], Mir Ali Hoda[19], Walter Klepetko[19], Aude Lacourt[20], Phil McElnay[21], Nick A. Maskell[22], Luciano Mutti[23], Jean-Claude Pairon[24], Paul Van Schil[25], Jan P. van Meerbeeck[12], David Waller[26], Walter Weder[3], Giuseppe Cardillo[27] and Paul Martin Putora[6,28]

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A European expert task force proposes updated and practical guidelines on routine management of malignant pleural mesothelioma, after a systematic review of the 2009–2018 literature (GRADE), including new promising therapies and strategies http://bit.ly/38876ta

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ABSTRACT The European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS)/European Association for Cardio-Thoracic Surgery (EACTS)/European Society for Radiotherapy and Oncology (ESTRO) task force brought together experts to update previous 2009 ERS/ESTS guidelines on management of malignant pleural mesothelioma (MPM), a rare cancer with globally poor outcome, after a systematic review of the 2009–2018 literature. The evidence was appraised using the Grading of Recommendations, Assessment, Development and Evaluation approach. The evidence syntheses were discussed and recommendations formulated by this multidisciplinary group of experts. Diagnosis: pleural biopsies remain the gold standard to confirm the diagnosis, usually obtained by thoracoscopy but occasionally *via* image-guided percutaneous needle biopsy in cases of pleural symphysis or poor performance status. Pathology: standard staining procedures are insufficient in ∼10% of cases, justifying the use of specific markers, including *BAP-1* and *CDKN2A* (*p16*) for the separation of atypical mesothelial proliferation from MPM. Staging: in the absence of a uniform, robust and validated staging system, we advise using the most recent 2016 8th TNM (tumour, node, metastasis) classification, with an algorithm for pre-therapeutic assessment. Monitoring: patient's performance status, histological subtype and tumour volume are the main prognostic factors of clinical importance in routine MPM management. Other potential parameters should be recorded at baseline and reported in clinical trials. Treatment: (chemo)therapy has limited efficacy in MPM patients and only selected patients are candidates for radical surgery. New promising targeted therapies, immunotherapies and strategies have been reviewed. Because of limited data on the best combination treatment, we emphasise that patients who are considered candidates for a multimodal approach, including radical surgery, should be treated as part of clinical trials in MPM-dedicated centres.

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Introduction

Malignant pleural mesothelioma (MPM) is a rare tumour that has become a world health issue due to its poor prognosis and its increasing incidence, largely due to prior asbestos exposure. However, there has been a remarkable improvement of the knowledge of MPM pathogenesis in recent years, leading to new potential drugs and strategies [1, 2]. Moreover, recent results from trials with multimodal treatment or innovative drugs such as targeted therapies or immunotherapies have brought new hope for MPM patients [3].

Optimal treatment in MPM has not previously been well defined and recent informative guidelines from the British Thoracic Society [4], the American Society of Clinical Oncology [5], the National Comprehensive Cancer Network (NCCN) [6] and the European Society for Medical Oncology [7] have reviewed similar published evidence and came to different conclusions and recommendations. This task force was conducted by the European Respiratory Society (ERS) in collaboration with the European Society of Thoracic Surgeons (ESTS), the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society for Radiotherapy and Oncology (ESTRO). It brought together experts on mesothelioma from different scientific societies to update the previous recommendations [8], with the aim of providing clinicians with a clear, concise and up-to-date statement on MPM management.

Methods

The purpose of these guidelines is to update the previous ERS/ESTS clinical practice guidelines for the management of MPM [8] and provide evidence-based recommendations for specialist care clinicians who want to offer patients a therapeutic approach based on radiotherapy, surgery, (chemo)therapy (first-line and salvage) or a combination of these modalities. Epidemiology, aetiology, biomarkers and screening of asbestos-exposed populations, clinical and pathological diagnosis and staging as well as treatment allocation have been summarised narratively and research priorities have been issued.

This current joint ERS/ESTS/EACTS/ESTRO task force was co-chaired by AS, IO, PMP and GC and included 28 clinicians with experience in several disciplines of MPM management and research and one European Lung Foundation representative (JB). One methodologist (DR) ensured that all the methodological requirements were met. The co-chairs and task force members discussed the evidence and formulated the recommendations; the methodologist did not participate in the development of recommendations. All panel members were required to disclose their conflicts of interest.

A first literature search was performed in November 2016 using the Ovid MEDLINE system. This research was performed by a scientific librarian (VD), experienced in searching for medical and scientific publications, and by physicians, experts in the treatment of thoracic neoplasms and trained in

Affiliations: [1]Pulmonary and Thoracic Oncology, Univ. Lille, CHU Lille, INSERM U1189, OncoThAI, Lille, France. [2]French National Network of Clinical Expert Centers for Malignant Pleural Mesothelioma Management (Mesoclin), Lille, France. [3]Dept of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland. [4]Thoracic Oncology Clinic, Institut Jules Bordet, Brussels, Belgium. [5]Oxford Centre for Respiratory Medicine, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. [6]Dept of Radiation Oncology, Kantonsspital St Gallen, St Gallen, Switzerland. [7]Iberoamerican Cochrane Center, Barcelona, Spain. [8]Dept of Thoracic Oncology, Pleural Diseases and Interventional Pulmonology, Hôpital Nord, Aix-Marseille University, Marseille, France. [9]Dept of Thoracic Surgery, Evang, Kliniken Essen-Mitte, Essen, Germany. [10]European Lung Foundation, Sheffield, UK. [11]Dept of Imaging and Pathology, KU Leuven, Leuven, Belgium. [12]Dept of Pulmonology and Thoracic Oncology, Antwerp University and Antwerp University Hospital, Antwerp, Belgium. [13]Dept of Radiation Oncology (Maastro Clinic), Maastricht University Medical Center+, GROW Research Institute, Maastricht, The Netherlands. [14]Bibliothèque des Sciences de la Santé, Université libre de Bruxelles (ULB), Brussels, Belgium. [15]The Christie NHS Foundation Trust, The University of Manchester, Manchester, UK. [16]Leicester Cancer Research Centre, University of Leicester and University of Leicester Hospitals NHS Trust, Leicester, UK. [17]National Reference Center for Pleural Malignant Mesothelioma and Rare Peritoneal Tumors MESOPATH, Dept of Biopathology, Centre Leon Berard, Lyon, France. [18]Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Inserm UMR1068, CNRS UMR7258, Dept of Multidisciplinary Oncology and Therapeutic Innovations, Marseille, France. [19]Dept of Thoracic Surgery, Medical University of Vienna, Vienna, Austria. [20]Univ. Bordeaux, INSERM, Bordeaux Population Health Research Center, team EPICENE, UMR 1219, Bordeaux, France. [21]Newcastle University, Newcastle upon Tyne, UK. [22]Academic Respiratory Unit, Bristol Medical School, University of Bristol, Bristol, UK. [23]Teaching Hosp. Vercelli/Gruppo Italiano Mesotelioma, Italy. [24]INSERM U955, Equipe 4, Université Paris-Est Créteil, and Service de Pathologies professionnelles et de l'Environnement, Institut Santé-Travail Paris-Est, CHI Créteil, Créteil, France. [25]Dept Thoracic and Vascular Surgery, Antwerp University and Antwerp University Hospital, Antwerp, Belgium. [26]Barts Thorax Centre, St Bartholomew's Hospital, London, UK. [27]Unit of Thoracic Surgery, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy. [28]Dept of Radiation Oncology, University of Bern, Bern, Switzerland.

Correspondence: Arnaud Scherpereel, Pulmonary and Thoracic Oncology Dept, CHU de Lille, F-59037 Lille Cedex, France. E-mail: arnaud.scherpereel@chru-lille.fr

evidence-based medicine. The Ovid MEDLINE database was searched using the OvidSP interface. The "Population, Intervention, Comparison, Outcome" (PICO) questions model for clinical questions was used to identify the concepts included in the questions, as shown in the supplementary material [9]. The corresponding search criteria were translated into Medical Subject Headings (MeSH) terms, free-text keywords and name of substances or interventions (supplementary material). Results were limited to articles published from 2009 to the present. It was a search strategy decision to limit the start of the search to 2009, after the previous ERS/ESTS guidelines, to restrict it to pertinent citations, as a systematic search of the literature up to 2008 was conducted by the previous task force. Citations were exported from MEDLINE into reference manager databases (EndNote) to allow the removal of duplicates and to facilitate the selection process performed by reviewers. All articles retrieved by the librarian were selected for their eligibility by two authors based on the title and abstract, and the final selection was performed by reading the full publication and its inclusion was decided by consensus. This search was supplemented by screening the references of the selected articles and other literature known to the experts.

An update of the literature was performed on January 2019 in order to capture randomised clinical trials relevant to the clinical questions. Supplementary figure S1 shows a flow chart of the literature search.

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to appraise the quality of evidence and to formulate, write and grade most recommendations. GRADEpro Guideline Development Tool software (McMaster University, 2015; developed by Evidence Prime, Hamilton, ON, Canada) was used to develop evidence profiles that summarised the findings for each outcome and the rationale for the quality of evidence appraisal [9].

The evidence profiles were sent to the task force members for review. Using an iterative consensus process conducted face to face, *via* teleconference and *via* email, recommendations were formulated on the basis of the following considerations: the balance of desirable (benefits) and undesirable consequences (burden, adverse effects and cost) of the intervention, the quality of evidence, acceptability and feasibility.

A strong recommendation for an intervention indicates that most well-informed patients would choose the intervention, whereas a conditional recommendation for an intervention indicates that well-informed patients may make different choices.

Thus, based on an extensive search of the literature (2009–2019) on MPM, the authors answered several questions on this cancer, to update previous European guidelines [8], including the following PICO questions:

Surgery

Should partial pleurectomy, compared to talc pleurodesis, be used as a palliative procedure in patients with symptomatic MPM?

Should "radical surgery" (including extrapleural pneumonectomy or pleurectomy/decortication) be used in patients with MPM?

Radiotherapy

Should radiotherapy be used for pain relief in patients with MPM?

Should radiotherapy be used to prevent procedure-tract metastases (drain site parietal seeding) in patients with MPM?

Should adjuvant postoperative radiotherapy be used in patients with MPM?

Medical treatment

Should first-line (chemo)therapy consisting of platinum alone or in combination with pemetrexed be used in patients with MPM?

Should bevacizumab be added to first-line standard (chemo)therapy in patients with MPM?

Should targeted therapies be added to first-line standard (chemo)therapy in patients with MPM?

Should immunotherapy be used as salvage therapy in patients with MPM who failed first-line standard (chemo)therapy?

Multimodality

Should a multimodal therapy approach (combining more than one method of cancer treatment: surgery, (chemo)therapy, radiation therapy) compared to (chemo)therapy alone be used in patients with MPM?

Epidemiology of mesothelioma

Incidence trend and predictions

From publications investigating the incidence trend at the world level, it appears that there is a lack of data regarding mesothelioma incidence and/or mortality for a large part of the world population [10–12] and especially for countries still using asbestos, such as in Eastern Europe, Asia, South America and most of Africa [13]. From available data, large disparities in mesothelioma incidence/mortality rates and trends are noticeable from country to country (supplementary table S1) [10–12, 14–43].

The pattern of mesothelioma incidence is highly correlated with the pattern of asbestos importation and use [14, 44] with a delay of ∼40 years due to the long latency period. It has been estimated that the incidence peak in Western Europe will be reached around 2020, and epidemiological data support these predictions [45]. Lower incidence rates in some parts of Asia and Central or Eastern European countries may be related to a poorer quality of data regarding diagnostic certification and registration [46] and a higher mortality from other causes. Besides, due to the long latency period, the epidemic of mesothelioma in those countries is likely to be at its beginning [13, 14].

The task force experts consider essential that all countries set up permanent epidemiological surveillance systems based on the exhaustive registration of mesothelioma cases at a national level.

Mesothelioma aetiology

Asbestos exposure

Asbestos is the principal aetiological agent of MPM. The term asbestos refers to six silicate minerals which are able to form very thin fibres, divided between the serpentine group (chrysotile) and the amphibole group of minerals (crocidolite, amosite, anthophyllite, tremolite and actinolite). Chrysotile is less biopersistent in the lungs than amphiboles. Chrysotile, amosite and crocidolite have all been widely used for industrial purposes.

To date, there are no new data questioning the previous guidelines [8]: 1) a dose–response relationship between asbestos exposure and mesothelioma occurrence has been demonstrated [47]; 2) however, it is still impossible to define a threshold of cumulative exposure below which there is no increased risk, implying that all exposed individuals are constituting a population at risk; and 3) the mean (range) latency of MPM following asbestos exposure is 40 (15–67) years [48].

Occupational asbestos exposure accounts for >80% of cases in males (supplementary table S2) [49–52] and the differences in attributable risk between males and females is probably due to household [53, 54] or environmental exposure (supplementary table S3) [51, 52, 55–74].

Exposure to other elongated mineral particles

Other elongated mineral particles such as erionite or fluoro-edenite may be involved in the aetiology of malignant mesothelioma (supplementary table S4) [75–94], with potential environmental exposure in various countries, such as Turkey, USA and Mexico [95–97].

From the available literature, occupational exposure to refractory ceramic fibres does not seem to be associated with the occurrence of MPM [88, 89]. However, some studies have raised the hypothesis of a synergistic effect between co-exposure to asbestos and other synthetic fibres, namely refractory ceramic fibres or mineral wool fibres [51, 98–100].

In 2014, in the absence of human data, multiwalled carbon nanotubes (MWCNT)-7 was classified by the International Agency for Research on Cancer (IARC) as possibly carcinogenic to humans (group 2B), while other sorts of carbon nanotubes were not classifiable as to their carcinogenicity to humans (group 3) [90, 94]. Recent experimental studies demonstrated the induction of MPM following intratracheal instillation of MWCNT into rat lungs [101, 102].

Genetic predisposition

Studies of familial aggregation of mesothelioma cases have reported an increased risk for subjects having parents and siblings diagnosed with mesothelioma [103–105]. Those observations led to the identification of a genetic component involved in the increased risk of mesothelioma in those families [106–112], namely a germline mutation of the BRCA1-associated protein (BAP)-1 gene, a tumour suppressor gene involved in the modulation of transcription and DNA repair. Other studies have attempted to identify new loci that might be associated with mesothelioma [111, 113–120].

A significant proportion of patients with malignant mesothelioma carry germline mutations in cancer susceptibility genes, especially those with peritoneal mesothelioma, minimal asbestos exposure, young age and a second cancer diagnosis [121, 122].

These data support clinical germline genetic testing for selected patients with malignant mesothelioma and provide a rationale for additional investigation of genetic pathways in malignant mesothelioma.

Other risk factors

Ionising radiation (mainly therapeutic radiation) is a risk factor for mesothelioma [123, 124], although it accounts for a small proportion of mesothelioma cases relative to asbestos exposure [13].

There were some controversies regarding the implication of the simian virus 40 (SV40) in MPM pathogenesis. In 2014, the IARC considered that SV40 could not be classified as carcinogenic to humans (group 3) [125]. It should be noted that tobacco smoking is not a risk factor for MPM.

The task force experts consider that national and international authorities must take an active role to achieve a complete and definitive ban of asbestos use worldwide, and to promote a close watch of other potential risk factors for MPM.

Biomarkers and screening in asbestos-exposed populations

Screening for MPM would raise many issues about the target population, the most efficient tool(s) to use, and, primarily, the rationale of such screening for a quite rare cancer.

Pleural plaques and MPM

Based on several consensus statements of an increased prevalence of pleural plaques among mesothelioma cases compared to non-mesothelioma subjects, the hypothesis of an association between pleural plaques and MPM has been raised [126–128]. However, since pleural plaques are considered a marker of asbestos exposure, it is not surprising to find such association and it is challenging to estimate the independent association between pleural plaques and MPM, considering that asbestos exposure is a strong confounder in this relationship. While most studies were based on chest radiograph detection of pleural plaques, recently, a positive and significant association between pleural plaques and MPM was found, detected using computed tomography (CT) scanning, while accounting for occupational asbestos exposure [129]. However, some authors have suggested that it cannot be ruled out that pleural plaques are only a marker of asbestos exposure [128].

Pleural plaques are likely to be a simple marker of previous asbestos exposure; the task force experts consider that no invasive diagnostic procedure is justified due to their presence. However, CT scans could detect (benign) asbestos-related lung diseases in exposed subjects, which may justify compensation according to national rules, but which may also be a marker of increased risk of MPM.

Research priority: the relationship between pleural plaques and MPM should be ascertained in large international epidemiological studies. The effectiveness of CT screening in the asbestos-exposed population should be determined in well-designed clinical trials.

(Diagnostic) biomarkers

Several blood biomarkers have been proposed for MPM screening, diagnosis, prognosis or follow-up during treatment. Results of biomarkers applied in populations for diagnosis purposes are summarised in supplementary table S5 [130–152]. The performance of these markers tested alone or in combination have been evaluated and reviews published [153–157]. A meta-analysis on the diagnostic value of soluble mesothelin in >4000 patients estimated sensitivity and specificity at 47% and 95%, respectively [135]. A few prospective studies conducted in subjects previously exposed to asbestos (supplementary tables S6 and S7) failed to demonstrate any value of serum mesothelin as a screening tool in these populations [158–164]. Simulations of real-life use of biomarkers (supplementary table S8) found a very high number of false-positive cases, even in populations highly exposed to asbestos. The role of mesothelin and other biomarkers for monitoring the response to antitumour treatment are currently being evaluated in a number of centres.

Research priority: routine determination of previously proposed biomarkers in MPM have no current validated role in diagnosis, prognosis or clinical follow-up (disease monitoring). Thus, further research into the role of biomarkers in these goals is required and highly encouraged.

Methods of assessing asbestos exposure

No significant change was found since the 2009 ERS/ESTS guidelines [8].

MPM compensation

As occupational asbestos exposure is strongly associated with the occurrence of mesothelioma, some countries have set up compensation programmes, *i.e.* recognition of MPM as an occupational disease [18, 165–167] and/or compensation from asbestos victims' funds [167]. An analysis of the literature [18, 165–167] suggests undercompensation for MPM cases.

The task force experts consider that the dissemination of information to clinicians and patients regarding the right to compensation for MPM should be reinforced according to the specific rules applying in each country.

Diagnosis of MPM

Clinical manifestations

The following recommendations from the 2009 ERS/ESTS guidelines are still valid in 2019 without any change according to the 2009–2017 literature [8].

The clinical manifestations of MPM are usually nonspecific and insidious and should not be used alone as diagnostic criteria, even in cases of previous asbestos exposure.

Chest radiography usually shows a unilateral pleural effusion and/or thickening. Chest radiography alone should not be used for the diagnosis of MPM. In addition, chest CT scan is unsuitable for definitive diagnosis of MPM, but diffuse or nodular pleural thickening is suggestive of the disease, especially involving mediastinal pleura. Chest CT scans with intravenous contrast agent (optimised for pleural evaluation) is the modality of choice for initial evaluation of patients with suspected MPM. Positron emission tomography (PET)–CT can be used to provide useful functional information on pleural lesions, if prior talc pleurodesis has not been performed, even if it not specific enough to diagnose MPM routinely. Functional magnetic resonance imaging (MRI) may be considered in these situations and other difficult diagnostic cases. MRI data appear promising, but are yet to be validated prospectively. The imaging modalities are the cornerstone of determining the correct biopsy site.

What is the best pleural biopsy method in suspected cases of mesothelioma?

Thoracoscopic biopsies (performed under local or general anaesthesia) are the gold standard for investigating an undiagnosed pleural effusion where the differential diagnosis includes mesothelioma. However, other biopsy methods are less invasive and may be more appropriate in selected cases. Thus, image-guided cutting-needle biopsies have high diagnostic rates and are particularly useful in patients with pleural thickening without associated pleural effusion, or in frail patients not fit enough for thoracoscopy. In particular, thoracic ultrasonography (TUS) allows the physician and radiologist to perform pleural biopsies more accurately and safely without any radiation exposure.

Blind closed-needle biopsies

The sensitivity of Abrams biopsies for malignancy is between 27% and 60% [168–172], being much lower for mesothelioma diagnosis. In the largest review of 2893 Abrams samples, diagnostic yield was only 57% for malignant disease [171]. Because of its poor yield, its use is diminishing in most developed countries and it cannot be recommended as a first-line investigation in this setting.

Image-guided pleural biopsy

The sensitivity of image-guided biopsy has been reported in a number of observational series, with both ultrasound- and CT-guided biopsies being superior to blind pleural biopsy [173, 174]. A prospective randomised trial comparing CT-guided cutting-needle biopsies with Abrams biopsy demonstrated that cutting-needle biopsies were 40% more sensitive at diagnosing malignancy [175]. The yield from CT-guided biopsy was 87%, compared with 47% for Abrams biopsies ($p=0.02$), with the added benefit of fewer passes of the needle in the image-guided group. This is important in cases of suspected mesothelioma where tumour seeding can occur along biopsy tracks.

A recent publication suggests that physician-led, ultrasound-guided pleural biopsy is effective, both as a planned procedure in patients not suitable for thoracoscopy, and as a secondary "on-the-table" option if thoracoscopy fails [176]. Diagnoses were obtained in 47 (94%) out of 50 patients. Out of 15 patients with a final diagnosis of malignancy, ultrasound-guided biopsy provided diagnostic material in 13 (87%).

Video-assisted thoracic surgery and medical thoracoscopy

Video-assisted thoracic surgery (VATS) and medical thoracoscopy plays an important role in the diagnosis of MPM. As well as securing a pathological diagnosis [177], it also allows evacuation of symptomatic pleural effusion and pleurodesis using talc poudrage [178]. In addition, it permits the assessment of the pleural cavity for staging purposes, in particular the assessment of visceral pleural and diaphragmatic pleural invasion, which are important prognostic factors [179].

Local-anaesthetic thoracoscopy or medical thoracoscopy

The diagnostic yield of medical thoracoscopy for pleural malignancy is high. Pooled results from 1369 patients in 22 case series showed an overall diagnostic sensitivity of 92% [180]. Medical thoracoscopy has been shown to be more successful at diagnosing malignancy than blind or image-guided Abrams biopsies [181–183], and had a higher diagnostic yield than CT-guided cutting-needle biopsies in one small randomised trial [184]. The complication rates are very low, with analysis of 47 studies including 4756

patients reporting a mortality rate of 0.34%, major complications in 1.8% and minor complications in 7.8% of cases [180].

VATS

VATS pleural biopsies carry a sensitivity of 95%, specificity of 100% and negative predictive value of 94%. This is similar to medical thoracoscopy, although no randomised trial has directly compared the two procedures. VATS offers the additional benefit of allowing the performance of more invasive surgical interventions, such as lung resection and tumour debulking, at the same time as the diagnostic procedure. It is important to note that VATS can be performed under local anaesthesia on nonintubated patients [185].

Tumour spread at resected previous chest tracts and scars is common and was identified as a negative prognosticator for long-term survival [186, 187]. Therefore, VATS (or medical thoracoscopy) incisions should be generally in line with possible forthcoming thoracotomy incisions [188]. This allows the resection of VATS (or medical thoracoscopy) tracts at the time of future surgery to avoid tumour recurrence in these areas [189, 190].

Open pleural biopsy

Sometimes, due to an obliterated pleural space secondary to locally advanced disease, VATS is not possible. In such cases, a small muscle-sparing incision within an intercostal space (with and without associated partial rib resection) allows for open pleural biopsy. CT- or TUS-guided cutting-needle biopsy is another option in this setting. Therefore, thoracotomy is usually not necessary for the accurate diagnosis of MPM.

Pathology

The diagnosis of mesothelioma is purely histological, based on an adequate tissue specimen and on international evidence-based comprehensive classification agreed by experts throughout the world. The World Health Organization (WHO) histological classification was updated in 2015 [191]. The development of recommendations for MPM pathology was not considered in the scope of these guidelines, because the European task force experts considered that the recommendations from the International Collaboration on Cancer Reporting and the recent update of the International Mesothelioma Interest Group consensus statement are applicable in this context [192, 193].

Clinical information is required for an accurate diagnosis by the pathologist, because it can influence the initial hypothesis, the processing of the specimen, the procedure of sampling and the ancillary analysis to be performed (immunohistochemistry (IHC), the choice of antibodies, fluorescence *in situ* hybridisation (FISH) analysis, RNA sequencing, comparative genomic hybridisation array, *etc.*).

Histopathological specimen examination according to MPM clinical presentation

As pleural effusion is usually the first clinical sign of MPM, cytology is often the first diagnostic procedure to be performed. However, most effusions are caused by the epithelioid type, since sarcomatoid mesothelioma does not usually shed cells into the serosal cavity [194]. Distinction from benign pleural lesions can be impossible on cytology alone, because subpleural fat tissue invasion, which is the most important criterion for malignancy, is lacking. However, recent tests based on molecular abnormalities can be valuable tools. Cytological suspicion of mesothelioma should be followed by tissue confirmation.

The International Mesothelioma Panel recommended that disease recurrence and metastases can be ascertained on cytology alone [193]. However, according to these latest guidelines, in patients unable to benefit from pleural tissue biopsies, a diagnosis of MPM could be ascertained on pleural effusion cytology alone when using specific ancillary techniques, and be as reliable as tissue biopsy, even if the sensitivity remains lower (30–75%). Thus, although cytology of pleural effusion is not recommended for obtaining an initial firm diagnosis of MPM, it may be very useful for differentiating MPM from other, more common malignancies, *e.g.* lung carcinoma. Cytology is more reliable if pleural exudate is preserved in cytoblocks and if ancillary tests (IHC or genetic testing, *e.g.* p16 deletion in FISH) can be performed [193, 195].

Therefore, as the production of cytoblocks is not a routine procedure in all institutions, the experts would like to highlight the necessity of preparing cytoblocks from pleural effusion samples.

Diagnosis of mesothelioma from fine-needle biopsies is associated with the same diagnostic constraints as pleural cytology, with a low sensitivity (30%) [196, 197]. A conclusive diagnosis can only be made if the material is representative of the tumour with sufficient quantity to allow IHC and FISH analysis characterisation in the context of appropriate clinical, radiological and/or surgical findings [198].

Macroscopy

The macroscopic aspect of mesothelioma varies during the natural history of the tumour. Therefore, the topography of the tumour is an important component for pathological staging. A diagnosis of diffuse MPM is more suggestive when the mesothelioma progresses and forms a rind of tumour encasing the lung. Nevertheless, other secondary or primary tumours may have a misleading pseudomesotheliomatous gross characteristic. The type of biopsy may affect the accurate typing and subtyping of diffuse MPM. In addition, it is important to know if the lesion is localised or diffuse, principally because (rare) localised MPM might benefit from surgical resection [194].

Microscopy

The task force experts consider the 2015 WHO classification reasonable, because it provides a comparative basis for diagnosis, prognosis and therapeutic management of the patient. However, it is well known that some epithelioid mesothelioma subtypes have a better prognosis (papillary, acinar, trabecular), while others have a worse prognosis (solid). Moreover, the presence of particular stromal responses (with abundant myxoid stroma or the rare lymphohistiocytoid variant) also has prognostic value. Some cytological features are associated with a poor outcome (pleomorphic and transitional). The current definition of biphasic mesothelioma requires that $\geqslant$10% of both epithelioid and sarcomatoid components be present. There is a consensus agreement that if the percentage of sarcomatoid component is <80% in the diagnosis of biphasic mesothelioma, it is correlated with a better prognosis. The evaluation of the percentage of the sarcomatoid component is restricted to resected tumours (large surgical specimens) and should not be evaluated on smaller samples [199].

Role of IHC

IHC enables the separation of different MPM subtypes from other malignancies or pleural metastases, using various sets of antibodies, with a relatively high diagnostic accuracy (supplementary tables S9–S11). In addition to these markers, claudin 4 has recently emerged as one of the most useful markers to separate mesothelioma (claudin 4-negative) from adenocarcinomas (claudin 4-positive) such as breast cancer metastases [193]. Furthermore, sarcomatoid mesothelioma may be cytokeratin-negative in 5% of cases and in 10% if heterologous elements are present; in this situation the diagnosis should only be made in the context of appropriate clinical, radiological and/or surgical findings [194].

The three well-defined genetic alterations in diffuse MPM are loss of *neurofibromatosis 2* (*Nf2*) by mutation or heterozygous or homozygous deletion, observed in 45–50% of cases; the homozygous deletion of the gene *CDKN2A* (*p16*) located on the 9p21 locus, reported in nearly 100% of sarcomatoid mesothelioma [200]; and loss (absence of nuclear staining when a positive internal control is present on the slide) of BAP-1 (a tumour suppressor gene located on 3p21 locus) by mutation, biallelic deletion or deletion/insertion, detected in 45–100% of diffuse MPM, mostly epithelioid subtype. While the loss of Nf2 has not proven to be useful in the IHC diagnostic routine [201], BAP-1 loss is a reliable marker on paraffin-embedded tissue and cytoblock section and is associated with a better prognosis. Loss of CDKN2A (p16) detected on formalin-fixed, paraffin-embedded sections as well as on cytoblocks using FISH is associated with a worse prognosis and observed with a sensitivity up to 50%, being higher in sarcomatoid mesothelioma. The presence of homozygous deletion of the CDKN2A (p16) by FISH analysis is extremely useful, specifically when subpleural fat tissue or lung parenchyma invasion are missing, and favours the diagnosis of malignancy if there is a strong clinical context and radiological evidence of a pleural tumoural process. However, it should be taken into account that BAP-1 loss and p16 are not 100% specific for mesothelioma.

The loss of BAP-1 expression and/or CDKN2A (p16) homozygous deletion may allow the discrimination of MPM from benign pleural lesions. Given the prognostic and therapeutic significance of BAP-1 loss, BAP-1 may be assessed first by IHC.

Electron microscopy is time- and resource-consuming, and is no more useful with IHC and FISH assays. Finally, freezing pleural tumour tissue is not required routinely, but it may be highly valuable for academic and translational research projects. If so, quality control of the specimen should be performed, and informed consent is needed for ethical biobanking.

Staging and prognosis assessment

8th TNM revision

The International Association for the Study of Lung Cancer (IASLC) mesothelioma staging project experts have updated their initial findings [202] using prospective data on >3500 patients treated both surgically and nonsurgically [203]. Their recommendations [204, 205] will inform the 8th revision of the American Joint Committee on Cancer/Union for International Cancer Control TNM staging system for mesothelioma, summarised here.

Clinical staging

T stage

T1a (parietal pleura) and T1b (visceral pleura) have been combined into one T1 classification with tumours involving the ipsilateral parietal or visceral pleura only. The T2 classification was used most often due to lung invasion or involvement of fissures. T4 stage was usually due to diffuse chest wall, diaphragm or transmural pericardial invasion. The most common deficiency of clinical staging was the failure to identify occult chest wall or pericardial invasion. In these cases, upstaging was demonstrated subsequently following surgery.

Exploratory analysis suggests that absolute measurement of pleural tumour thickness correlates with survival. When measurements of maximal thickness at upper (apex to inferior margin of aortic arch), middle (between upper and lower) and lower (inferior to left atrium) zones were taken, both the maximum thickness at any level or the sum of the thickness were prognostic. Pleural thickness (maximum or sum) correlated with T stage and nodal positivity [204].

Research priority: prospective data collection about the measurement of tumour thickness or volume is to be encouraged.

N stage

The IASLC staging project found no difference in survival between clinical stages N0, N1 and N2 [206]. Clinical staging underestimated N status, subsequently found at surgery, in 33% of cases and overestimated it in 6%. Nodal size and the likelihood of malignant involvement have not been found to be correlated [207]. Nodal stage may be predicted from tumour volume. Patients with tumour maximal thickness of <5.1 mm had a 14% risk of nodal metastases, whereas this risk rose to 38% in patients with tumours of maximal thickness >5.1 mm ($p<0.0001$) [204].

Invasive mediastinal nodal staging with endobronchial ultrasound (EBUS) or mediastinoscopy can aid clinical staging, but clinicians should be aware that it may not be possible to access all nodal disease, extramediastinal areas (*i.e.* internal mammary), peridiaphragmatic or intercostal areas.

Task force experts consider that the use of noninvasive imaging is inaccurate in the assessment of nodal metastasis, and even direct biopsy may not exclude occult nodal disease. Therefore, clinicians should be aware of the implications of these staging limitations when discussing pretreatment prognosis.

M stage

The IASLC project evaluated only 84 cM cases, which nevertheless had sufficiently poorer prognosis than cT4 cases to be considered as the only descriptor in the stage IV classification. Exploratory analyses suggested a possible difference in survival for single- *versus* multiple-site cM1 cases [205].

Task force experts consider that it is important to exclude occult distant metastases if radical therapy is considered due to poor prognosis associated with stage IV.

Pathological staging

T stage

There appear to be no survival differences between pT1, pT2 and pT3, but there was between pT3 and pT4 (hazard ratio (HR) 1.34, $p<0.0005$) [204]. The classification of pT3 was most often due to partial-thickness pericardial invasion, and pT4 was most commonly due to diffuse chest wall involvement. Other variables that may have prognostic significance include tumour involvement of previous biopsy or incision sites [186, 208] and the weight of tumour resected [209].

Clearly marked anatomical structures (pericardium, chest wall biopsy sites) on resection allow accurate pathological orientation and staging, particularly in lung-sparing operations. Any previous biopsy site should always be excised and submitted for histology.

N stage

The pattern of lymphatic drainage of the pleura does not follow the same pathway as for the lung parenchyma; mediastinal nodes may be the initial site of metastases before the lung parenchyma is involved. Traditional pN2 may therefore precede pN1.

The IASLC staging project reported no survival difference between pN1 and pN2. Therefore, clinical and pathological N1 and N2 are combined into a single N1 category including all ipsilateral, intrathoracic nodal metastases. Contralateral or all extrathoracic nodal metastases are then categorised as N2 [206].

The importance of extramediastinal nodal metastases in the intercostal and peridiaphragmatic groups remains unknown due to paucity of data. The proportion of involved *versus* normal lymph nodes has been found to be more prognostic than anatomical location [210].

Pretreatment staging investigations

The stage of the disease determines whether the direction of intervention is cancer-directed (in order to prolong cancer-specific survival) or merely palliation of symptoms. This decision of how extensive the staging measures are will be determined by an initial assessment of the patient's fitness for either surgery or (chemo)therapy. Other factors include the underlying cell type of the tumours (epithelioid *versus* non-epithelioid) and the TNM staging.

Noninvasive staging

A summary of noninvasive staging is presented in figure 1.

Semiautomated tumour volume calculations on chest CT scan have correlated volume with pTN stages and overall survival [211].

Fludeoxyglucose (FDG)-PET is limited in the assessment of nodal stage due to the close proximity of diseased pleura, masking uptake. Moreover, previous chemical pleurodesis might affect FDG uptake and maximum standard uptake value (SUV_{max}) measurement. However, it may be useful in the identification of occult distant metastatic disease. PET-CT had low sensitivity for stage N1 (38%) and T4 (67%) disease [177]. PET-CT had a higher specificity for stage II (77% *versus* 100%, p<0.01) and stage III (75% *versus* 100%, p<0.01) disease compared to CT alone [212]. SUV_{max} may be of prognostic significance, even in unresectable disease [213].

MRI may be useful at the margins of the disease: the apex around the subclavian vessels, inferiorly around the diaphragm in order to demonstrate unresectable, multifocal chest wall invasion [177]. Although MRI is superior for detection of brain metastases and bone invasion, this technique was not superior to CT in terms of detection of lymph node metastases (p=0.85) and visceral pleural tumour (p=0.64). PET-MRI may be at least as accurate as PET-CT in staging [214], whereby radiologists felt significantly more confident staging PET-MRI compared to PET-CT using dedicated sequences. Further applications of functional MRI remain research areas only at present [215].

Invasive staging

A concurrent mediastinal nodal biopsy technique by mediastinoscopy has been described [216].

While extramediastinal nodes are anatomically inaccessible, there may be some benefit in excluding those with positive upper mediastinal nodes, as they carried a worse prognosis than lower or extramediastinal areas [208].

EBUS has been found to have superior sensitivity and negative predictive value to mediastinoscopy for nodal disease in MPM. However, values were both <60% for EBUS [217]. The theoretical additional yield

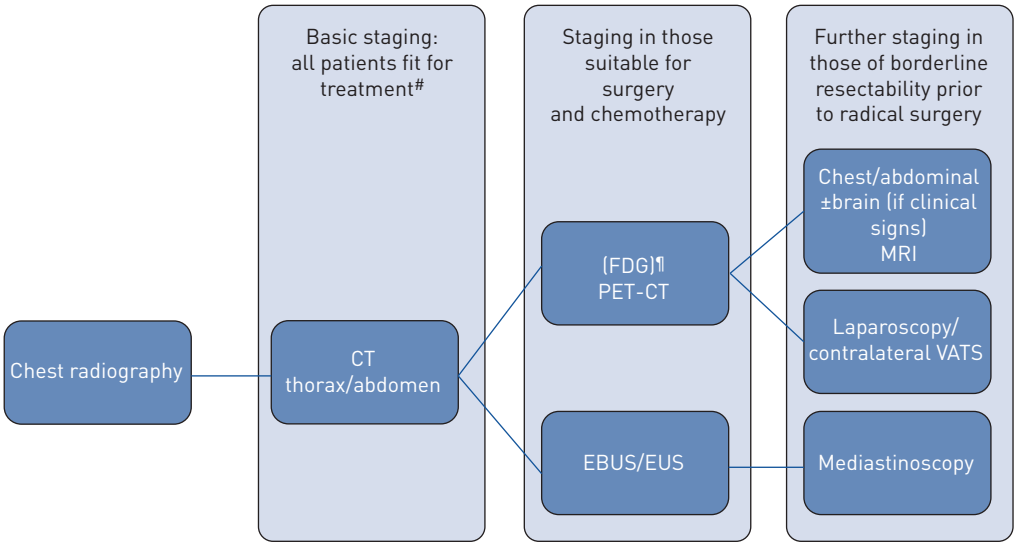

FIGURE 1 A summary of staging algorithm for patients with malignant pleural mesothelioma. #: patients unfit for any treatment could derive some benefit from basic computed tomography (CT) scan in terms of palliative therapy (pleurodesis) or reparation; ¶: after talcage, positron emission tomography (PET)–CT is less accurate than functional magnetic resonance imaging (MRI). FDG: fludeoxyglucose; EBUS: endobronchial ultrasound; EUS: endoscopic ultrasound; VATS: video-assisted thoracic surgery.

from EBUS in stations not accessible to mediastinoscopy was 26%, with a mean survival not significantly worse than those within range of mediastinoscopy. Those with only extramediastinal lymph node metastases had a significantly better survival than either of the above groups [218].

EBUS/endoscopic ultrasound (EUS) followed by simultaneous transcervical extended mediastinal lymphadenectomy and laparoscopy/peritoneal lavage revealed only a small number of undetected nodal metastases that were not found by EBUS/EUS, and the majority of those with positive laparoscopy also had positive mediastinal nodes. This algorithm did not include PET-CT [219].

More invasive techniques including contralateral thoracoscopy and laparoscopy have been infrequently used and are difficult to appraise [220]. They have been shown to help identifying occult stage IV disease not seen on PET-CT.

The task force experts consider that the algorithm proposed in figure 1 is a reasonable approach for pretreatment staging investigations. However, it is not intended as a recommendation for clinical practice.

Research priority: the prospective use of volumetric assessment software should be encouraged.

Which other prognostic factors are of importance?

There is consistent evidence that cell type of MPM is of prognostic significance with epithelioid tumours offering superior survival to non-epithelioid subtypes.

Several nonanatomical prognostic variables can be used to influence the selection of treatment including chest pain, weight loss and dyspnoea, leading to poor performance status, anaemia, leukocytosis and thrombocytosis [221]. Composite prognostic scoring indices have been derived by several organisations including the European Organisation for Research and Treatment of Cancer (EORTC) [222] and Cancer and Leukemia Group B (CALGB) [223] to categorise patients and guide treatment decisions. Specific prognostic scores for surgically resected disease have also been calculated using similar variables: tumour volume pre-(chemo)therapy, C-reactive protein (CRP) level, nonepithelioid histology and progressive disease according to modified Response Evaluation Criteria in Solid Tumours (RECIST) criteria after induction (chemo)therapy [224].

Another simple, clinically relevant model, called the Brims score [225], was proposed to evaluate patients' prognosis using routinely available parameters at the time of diagnosis. This model defined four risk groups with significant different outcomes ($p<0.0001$). The strongest predictive variable was the presence of weight loss. Risk group 1 included the patients with the best survival at 18 months (86.7% alive, median overall survival (overall survival) of 34.0 months); these patients had no weight loss, a haemoglobin level >153 $g{\cdot}L^{-1}$, and a serum albumin level >43 $g{\cdot}L^{-1}$. Risk group 4d had the worst outcome (0% alive, median survival 7.5 months); these patients had weight loss, a performance score 0 or 1, and sarcomatoid histological MPM subtype.

Finally, the PROMISE score was proposed recently as a prognostic score in cohorts of patients with malignant pleural effusion in which a number of patients had mesothelioma [226].

The task force experts consider that prognostic factors and scoring systems may help in the decision process, but cannot usually be applied *per se* on an individual basis outside clinical trials, as they were not validated for this purpose.

Research priority: the routine use of the Brims score is encouraged, and combined with other scores as part of clinical trials for prospective validation.

In the future, patient-reported outcome measures may potentially improve the management of MPM based on a recent literature survey [227]. There is also a need to derive predictive factors of (chemo)therapy.

Treatment of MPM

Surgery for MPM patients

Should partial pleurectomy compared to talc pleurodesis be used as palliative procedure in patients with symptomatic MPM?

Our systematic review identified one randomised controlled trial (MesoVATS trial) [228] that compared partial pleurectomy (PP) by VATS *versus* talc pleurodesis in patients with MPM. The MesoVATS trial was an open-label randomised controlled trial conducted in 12 centres in the UK. The primary outcome was overall survival at 1 year. There were no differences between groups in the overall survival at 1 year (HR 1.04, 95% CI 0.76–1.42) nor at 6 months follow-up. Surgical complications were significantly more common after VATS-PP than after talc pleurodesis, occurring in 24 (31%) out of 78 patients who completed VATS-PP *versus* 10 (14%) out of 73 patients who completed talc pleurodesis ($p=0.019$). Median (interquartile range) hospital stay was longer at 7 (5–11) days in patients who received VATS-PP compared with 3 (2–5) days for

those who received talc pleurodesis (p<0.0001). However, the proportion of patients with resolved pleural effusion was significantly higher in the PP group than in the talc pleurodesis group at 1 month (37% *versus* 59%), but not at 3 months (60% *versus* 60%) or 12 months (77% *versus* 70%), although these numbers were based on surviving patients and heavily influenced by the attrition of follow-up (supplementary table S14). Furthermore, the benefits of VATS-PP (better quality of life, less short-term pleural effusion) do not balance the inconveniences (more leaks and cost). These data do not support a change of practice.

Recommendation: we recommend talc poudrage *via* thoracoscopy to control a recurrent MPM effusion as the first choice to achieve pleurodesis in patients with expanded lungs (strong recommendation, low quality of evidence).

We suggest palliative VATS-PP to obtain pleural effusion control in symptomatic patients fit enough to undergo surgery who cannot benefit from (or after failure of) chemical pleurodesis or indwelling catheter (weak recommendation, low quality of evidence).

Should radical surgery (including extrapleural pneumonectomy or pneumonectomy/decortication) be used in patients with MPM?

Radical surgery in MPM is defined as macroscopic complete resection, which can be achieved by extrapleural pneumonectomy (EPP) consisting of *en bloc* resection of pleura, lung, pericardium and diaphragm combined with systematic mediastinal lymph node dissection, or (extended) pleurectomy/decortication (P/D) and systematic mediastinal lymph node dissection. P/D is a resection of the total parietal and visceral pleurectomy, sparing the pericardium and the hemidiaphragm, while extended pleurectomy/decortication (EP/D) includes the resection of the pericardium and the hemidiaphragm, when required, and in order to remove all the macroscopic disease [229].

Whereas population and cancer registries consistently report a better outcome for surgically treated patients, they do not correct for prognostic factors, or do so incompletely, and are hence subject to patient selection and recall bias [230–235].

Our systematic review identified one randomised controlled trial (Mesothelioma and Radical Surgery (MARS) trial) [236] and two observational studies [237, 238] that compared surgical to nonsurgical therapeutic approaches in patients with MPM. The MARS trial was designed as a feasibility study and underpowered to assess any benefit (or absence thereof) of EPP. The low number of patients and the number of registered events was very limited; these features decreased the panel's confidence in the estimated effects to low. The study showed that the adjusted HR for overall survival between the EPP and no-EPP groups was 2.75 (95% CI 1.21–6.26). At a median follow-up of 24.7 months from randomisation, 30 out of 50 patients had died (EPP n=17; no EPP n=13); thus, the analysis of survival included only 30 deaths. The 12-month recurrence-free survival in the EPP group was 34.8% (95% CI 16.6–53.7%) compared to 42.3% (95% CI 23.5–60.0%) in the no EPP group, although the difference was not statistically significant. There were no statistically significant differences in those patients who completed the quality-of-life assessment (EPP n=12; no EPP n=19), although the median quality-of-life scores seemed to be lower for the EPP group than the no-EPP group. 12 serious adverse events were reported during the study period: 10 in the EPP group and two in the no-EPP group. Further critical problems are that the total number of patients achieving the trimodality approach was very low, and a relevant number of no-EPP patients received EPP (supplementary table S15).

These results differ from a large retrospective cohort of 1365 consecutive patients with MPM, suggesting that patients with good prognostic factors (*i.e.* age <70 years, epithelioid histology) have similar survival, whether they receive medical therapy only, P/D or EPP [237] (supplementary table S16).

Another retrospective study in 150 patients showed a nonsignificant trend to better overall survival and disease-free survival in those patients undergoing surgical resection (P/D or EPP) [238].

One bias of retrospective studies is that the choice of P/D or EPP depends largely on the institutions' experience, because of a huge variability of outcomes reporting regarding morbidity, mortality, quality of life and overall and disease-free survival. Therefore, due to the low overall confidence and the conflicting results between studies, the panel did not consider issuing a recommendation until more consistent data become available. A multicentre randomised trial comparing extended P/D to no surgery (MARS-2 trial) is currently recruiting in the UK [239]. Results from this surgical trial are awaited with interest.

Research priority: patients considered for radical surgery should be either included in prospective randomised controlled clinical trials or in national/international surgical registries.

Remark: surgery may be appropriate for carefully and highly selected MPM patients. This would usually be EP/D rather than EPP, because of its lower comparative respiratory postoperative morbidity and

preservation of quality of life, performed in centres of excellence and as part of multimodality treatment. Patients with sarcomatoid or sarcomatoid-predominant histology, N2 disease (8th edition TNM staging system) and/or stage IV should not be considered for radical surgery other than in the context of research. However, as no single prognostic factor influences treatment allocation, prognostic scores encompassing several prognostic factors should be preferred (see sections on staging and allocation).

Radiotherapy of MPM

Should radiotherapy be used for pain relief in patients with MPM?

Evidence from randomised controlled trials is not available for palliative radiotherapy in MPM. A prospective multicentre single-arm study [240] investigating 20 Gy in five fractions to painful areas in 40 patients demonstrated that radiotherapy can be effective in treating pain in selected mesothelioma patients (number needed to treat=2). Despite very limited data in the setting of MPM, the role of radiotherapy in pain control for other solid tumours has been demonstrated and is accepted in clinical routine [241–243].

Recommendation: we suggest that palliative radiotherapy for pain relief should be considered in cases of painful sites of disease caused by local infiltration of normal structures (moderate recommendation, low quality of evidence).

Should radiotherapy be used to prevent procedure-tract metastases (drain site parietal seeding) in patients with MPM?

Randomised controlled trials investigating prophylactic drain site radiotherapy in MPM have shown contradictory results. Boutin *et al.* [244] previously showed that an irradiation with 21 Gy in three fractions for three consecutive days in the 4 weeks following drainage or thoracoscopy prevents subcutaneous metastasis developing along drainage channels or thoracentesis tracts. However, a subsequent randomised trial was published comparing immediate drain site radiotherapy 21 Gy in three fractions to no radiotherapy in 61 patients treated between 1998 and 2004, with no difference in terms of tract metastatic recurrence between the two arms [245, 246]. O'Rourke *et al.* [245] concluded that prophylactic drain site radiotherapy in MPM did not reduce the incidence of tumour seeding as indicated in previous studies [247, 248].

Since the last guideline, two further randomised studies were not able to demonstrate a benefit with prophylactic tract irradiation. A multicentre phase III trial [249] compared immediate radiotherapy (21 Gy in three fractions within 42 days of the pleural intervention) with deferred radiotherapy (same dose given within 35 days of diagnosis of procedure-tract metastases (PTM)); 203 patients were randomised. There was no significant difference in terms of PTM rate, chest pain, quality of life, analgesia requirements or survival. However, there was a suggestion of a benefit in two predefined subgroup analyses, *i.e.* patients with epithelioid-only histology and those who did not receive (chemo)therapy (supplementary table S17).

The applicability of these findings is limited by the small numbers, thus further studies in these specific subgroups may be warranted. A further multicentre phase III randomised trial randomised 375 patients to prophylactic irradiation of tracts (21 Gy in three fractions within 42 days of the pleural intervention) or not. At 12 months, the rate of tract recurrence was 8.1% *versus* 10.1%, respectively (p=0.59) [250]. Prophylactic radiotherapy did not have a statistically significant reduction on the risk of procedure site recurrence, with a pooled relative risk of 0.64 (95% CI 0.27–1.51).

While the results of these two large randomised controlled trials can be considered contradictory to older and smaller trials of the pre(chemo)therapy era, the limited effects of radiotherapy to the prophylactic drain sites observed in these UK phase III trials do not justify this procedure in routine practice.

Recommendation: we do not recommend prophylactic drain site radiotherapy in routine clinical care (strong recommendation, moderate quality of evidence).

Should adjuvant postoperative radiotherapy be used in patients with MPM?

The 17/04 SAKK trial (Neo-adjuvant Chemotherapy and Extrapleural Pneumonectomy of MPM With or Without Hemithoracic Radiotherapy) randomised 54 patients post-EPP to observation *versus* adjuvant (minimum dose of 50 Gy with daily fraction size of 1.8–2 Gy) [251]. The trial closed earlier than planned due to poor accrual. Radiotherapy was associated with slightly better median locoregional relapse-free survival (9.4 months *versus* 7.6 months); however, this was not statistically significant (supplementary table S18).

A phase I/II trial has demonstrated that a short accelerated course of high-dose hemithoracic intensity-modulated radiation therapy (IMRT) followed by EPP is feasible [252]. Patients received 25 Gy in five daily fractions over 1 week to the entire ipsilateral hemithorax with concomitant 5 Gy boost to areas at risk followed by EPP within 1 week of completing neoadjuvant IMRT. Patients with epithelioid histological subtypes had a

3-year survival of 84% after a median follow-up of 23 months. While these results are encouraging and warrant further investigation, this approach is considered experimental at this point. Radiation therapy after lung-sparing surgery might be another approach, resulting in promising survival data [253].

A phase II study [254] demonstrated that hemithoracic pleural IMRT for MPM is safe and has an acceptable rate of side-effects. Its incorporation with (chemo)therapy and P/D forms a new lung-sparing treatment paradigm for patients with locally advanced MPM, but randomised trials are needed to potentially establish this in clinical routine.

Research priority: radiotherapy after pleurectomy±decortication or after EPP should only be considered within the context of clinical trials and/or included in national/international surgical registries.

Medical treatment of MPM

Some phase II and III trials have been completed in first-line and salvage therapy since the 2009 ERS/ESTS guidelines [255]. They are presented in supplementary tables S12 [256–274] and S13 [256, 259, 260, 275–290].

Should first-line (chemo)therapy consisting of platinum in combination with pemetrexed be used in patients with MPM?

No innovative drug has been validated in MPM since 2009 [255].

Recommendations (unchanged after the previous guidelines [8]): we recommend first-line combination (chemo)therapy consisting of platinum and pemetrexed (with folic acid and vitamin B12 supplementation) in patients fit for (chemo)therapy (good performance status, ECOG performance status 0–2, no contraindications) (strong recommendation, low quality of evidence).

Remarks: the administration of (chemo)therapy should not be delayed and should be considered before the appearance of functional clinical signs (or clinical deterioration). Chemotherapy should be stopped in the event of progressive disease, grade 3–4 toxicities or cumulative toxic doses, but should be continued up to six cycles in patients who respond or are stable.

Research priority: patients demonstrating prolonged symptomatic and objective response with first-line pemetrexed-based (chemo)therapy may be treated again with the same regimen in the event of recurrence. In the remainder of cases, inclusion of the patients in clinical trials is highly encouraged.

Should bevacizumab or other targeted therapies be added to first-line standard (chemo)therapy in patients with MPM?

In 2009, the guidelines task force concluded that immunomodulating agents, targeted therapies and vaccines should not be used in the treatment of MPM outside clinical trials. Many targeted therapies have been assessed in MPM since this time (reviewed in [2, 3]), including mainly antiangiogenic drugs and other growth factor inhibitors.

A large (n=448), phase III trial (Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS)) showed benefit in adding bevacizumab to cisplatin (cis)/pemetrexed (pem) doublet as first-line treatment [271] with significantly longer survival (primary end-point) (HR 0.67, 95% CI 0.61–0.94; p= 0.015) and a 2-month increase in progression-free survival (PFS) (HR 0.61, 95% CI 0.50–0.75; p<0.0001) favouring the bevacizumab arm, with only a mild and manageable increase of toxicity and no negative impact on quality of life. This study suggested a new standard of care for unresectable MPM patients, as validated by some US (NCCN) and French guidelines. However, to date, bevacizumab has not received US Food and Drug Administration or European Medicines Agency approvals in MPM because the French Cooperative Thoracic Intergroup MAPS trial was an academic trial, not initially designed for registration purposes (supplementary table S20).

No other antiangiogenic drug or tyrosine kinase inhibitors has yet demonstrated significant efficacy in a randomised phase III trial [3]. Thus, nintedanib, a drug targeting vascular endothelial growth factor receptor 1–3, platelet-derived growth factor receptor-α/-β and fibroblast growth factor receptor 1–3 failed to show any value in the phase III LUME-Meso trial [291] despite previous promising results in a randomised phase II trial *versus* placebo in conjunction with first-line cis/pem [292] with significant improvement in median PFS (HR 0.54) and in median overall survival (HR 0.77) (supplementary table S21).

Other main targeted drugs evaluated in MPM included vorinostat, an inhibitor of histone deacetylases, which failed to show any survival advantage *versus* placebo as second- or third-line treatment in a large phase III trial [284]. The phase II COMMAND trial (NCT01870609), assessing the focal adhesion kinase inhibitor VS-6063/defactinib *versus* placebo as maintenance treatment after first-line cis/pem, did not meet its primary goals (median PFS and median overall survival) [293]. Other promising drugs include pegylated arginine deaminase (ADI-PEG 20), in combination with cis/pem, targeting arginosuccinate

synthetase-1-deficient tumours such as biphasic (mixed) or sarcomatoid MPM [294]; the loss of BAP-1 may induce the sensitivity of MPM cells to therapies targeting the EZH2 pathway.

Recommendation: we suggest that bevacizumab, if available, be proposed in combination with cisplatin/pemetrexed as first-line treatment in patients fit for bevazucimab and cisplatin, but not for macroscopic complete resection (weak recommendation, moderate quality of evidence).

Should immunotherapy be used as salvage therapy in patients with MPM who failed first-line standard (chemo)therapy?

Since 2009, new immunotherapies have been tested in MPM, in particular immune checkpoint inhibitors such as anti-CTLA-4 (ipilimumab, tremelimumab), anti-PD-1 (pembrolizumab, nivolumab) and anti-PD-L1 (durvalumab, avelumab). Tremelimumab failed to show any survival improvement *versus* placebo as second-line treatment in a phase III trial [289] (supplementary table S22). In preliminary data from small nonrandomised trials, anti-PD-1 or anti-PD-L1 antibodies seemed to induce increased overall response rate and overall survival compared to historical second- or third-line chemotherapies [3, 295]. PROMISE MESO (NCT02991482), a phase III trial comparing pembrolizumab *versus* either vinorelbine or gemcitabine, has completed enrolment. CONFIRM (NCT03063450), a phase III double-blind randomised trial evaluating nivolumab *versus* placebo is ongoing [3, 296]. Moreover, in the same setting, nivolumab alone or combination of nivolumab plus ipilimumab significantly increased the disease control rate after 12 weeks of treatment and overall survival in a randomised phase II trial [297]. This combination was also efficient in another mono-arm phase II trial as second- or third-line treatment for MPM [298]. Durvalumab and tremelimumab combination may also have a therapeutic value in MPM patients, based on a first report [299]. Finally, preliminary reports of first-line (chemo)therapy plus anti-PD-1 or anti-PD-L1 are promising [300].

Several other trials are ongoing [301], assessing immunotherapies, alone or combined with (chemo) therapy and/or targeted therapies (anti-angiogenic, epigenetic drugs), as first-line or salvage therapies. Interestingly, cell therapy (with dendritic cells, chimeric antigen receptor (CAR) T-cells) or gene therapy trials are also currently recruiting MPM patients.

Research priority: novel insights in immunotherapy are promising, but need further development and results from ongoing or planned phase III trials before any definitive recommendations can be made for their use in the clinical routine. Inclusion of patients in these trials is highly recommended.

What assessment criteria should be used to determine the efficacy of systemic treatment in MPM?

No specific significant data have been published since the previous guidelines [255]. The activity of a treatment can be assessed on clinical criteria (symptoms control and quality of life), imaging criteria (CT scan, PET scan) and survival criteria (time to progression, overall survival).

Overall survival is not the only valuable parameter to assess the effectiveness of medical treatment in clinical trials. It is recommended that quality of life and symptom control be taken into account, to evaluate the clinical benefit (efficacy/tolerance) in diseases with poor prognosis and for which the survival impact of the treatment is not clearly demonstrated or is marginal. No particular score to assess quality of life is recommended specifically, except the modified version of the Lung Cancer Symptom Scale adapted to patients presenting with malignant mesothelioma.

For clinicians MPM is characterised by obstacles in tumour measurement and response assessment. To help them in routine practice as well as in the conduct, interpretation and reporting of clinical trials, the modified RECIST was proposed in 2004. However, the practical application of these criteria was tricky, leading to misinterpretation and inconsistencies in tumour response assessment. Therefore, the modified RECIST 1.1 for mesothelioma [302] were proposed recently to provide updated response assessment guidelines improving previous criteria but also aiming at better defining crucial concepts for MPM, such as minimally measurable disease, measurable lesions, acceptable measurement location or nonmeasurable pleural disease. In addition, they may help to better evaluate nonpleural disease, pathological lymph nodes and bilateral MPM and to establish progressive disease.

Even if they have not been prospectively validated, the task force experts consider the updated modified RECIST 1.1 guidelines the preferred method of choice for measuring tumour lesions and response to treatment on CT scans. If a patient has had pleurodesis, it has been strongly suggested that a chest CT scan should be repeated before the start of (chemo)therapy in order to better evaluate the response to treatment. In fact, pleural lesions may be better described after removal of pleural effusion, favouring a correct assessment of patient outcome. PET scan and biological markers are still under investigation for the evaluation of treatment response in MPM.

Should a multimodal therapy approach (combining more than one method of cancer treatment: surgery, (chemo)therapy, radiation therapy) compared to (chemo)therapy alone be used in patients with MPM?

In order to address the role of multimodality therapy in MPM, the following clinical questions were raised. Is multimodality treatment better than (chemo)therapy alone? What is the optimal regimen within each modality? What is the optimal sequence of interventions within a combined modality approach? However, since 2009, our systematic review of the literature, as well as two other recent reviews [303, 304] only identified two randomised clinical trials on the topic: MARS and SAKK 17/04 [236, 251]. Both trials have been considered in other sections of these guidelines (radical surgery and postoperative radiotherapy), without mentioning that they were assessing multimodality options, leading the task force to only issue research priorities. These two trials had many weaknesses. For example, the MARS study was a feasibility trial that did not reach the prespecified sample size [236]; multimodality treatment was compared to continued oncological management, which could include (chemo)therapy and palliative radiotherapy [236], or (chemo)therapy and surgery [251]. Median overall survival observed in both studies was less than expected when compared with observational data; this result might partly be explained by the inclusion of patients with worse prognosis. Globally, these trials involved limited number of patients and events, and wide 95% confidence intervals that included appreciable harm or benefit (supplementary tables S15 and S18).

Thus, as emphasised by other recent reviews [303, 304] or guidelines [4–6], the literature remains biased for multimodal management of MPM patients, without high quality of evidence in favour of a specific therapeutic combination or scheme. Multimodal treatment consisting of at least macroscopic complete resection and (chemo)therapy (platinum/pemetrexed doublet), was superior to either single modality in selected patients with regard to survival, but at the cost of increased treatment-related morbidity and mortality [304]. Given the added cost of multimodality strategies, the possible increase in risk of adverse effects and the lack of evidence of their effectiveness, the Cochrane review authors also concluded that these interventions should not be proposed in routine clinical practice.

Research priority: we still recommend that patients who are considered candidates for a multimodal approach should be adequately informed of its challenges and referred to expert centres in order to be included in a prospective (randomised) clinical trial and/or registered in a large institutional database.

Treatment allocation

This question, as well as the global management of MPM patients, is summarised by the algorithm presented in figure 2. Counselling patients for the most appropriate and promising treatment, balancing life expectancy with quality of life remains a difficult issue, despite the development of a more detailed TNM staging [200, 305, 306], progress in staging tools and improved knowledge of tumour biology. In contrast to most other malignancies, the discrepancy in reliability between clinical and pathological staging leads quite frequently to an unsatisfactory patient selection for multimodality treatment including radical surgery. When radical surgery (usually P/D) is considered, clinical and functional assessment should be undertaken as described above, including at least spirometry, diffusion capacity of the lung for carbon monoxide, and cardiovascular assessment. CT, PET-CT and/or MRI are used to exclude distant metastasis and evaluate resectability. Thus, the decision whether radical surgery is recommended should be based on a number of different aspects. It has been shown in various studies [211] that tumour volume, measured preoperatively on CT scans, predicts pT/pN and overall survival. Other single factors such as mediastinal nodal involvement or histology available preoperatively (see staging section) predict overall survival. Despite an increasing knowledge about molecular markers and their diagnostic and prognostic value, they are not yet used for treatment allocation. Not surprisingly, single factors are insufficient for proper treatment allocation, and prognostic scores have been developed. The EORTC and the CALGB [222, 223] scores were developed for better identification of patients receiving (chemo)therapy. Prognostically relevant "CORE" covariates (stage, sex, age, histology and type of surgery) were evaluated for patient selection [221]. A multimodality prognostic score based on tumour volume, histology, CRP at diagnosis, nodal status and response to (chemo)therapy allows the identification of patients with very poor prognosis despite multimodality therapy [224]. In conclusion, several prognostic scores have been proposed for treatment allocation of MPM patients. But to date, no single parameter or score has been widely validated for routine use for this purpose.

Research priority: current and future scores suggested for patient treatment allocation, always decided by an MPM expert multidisciplinary board, require prospective validation by multicentre studies.

Palliative care

The control of malignant pleural effusion (MPE) is not detailed in these guidelines, as it is fully explained in the new ERS/EACTS guidelines on MPE management [307].

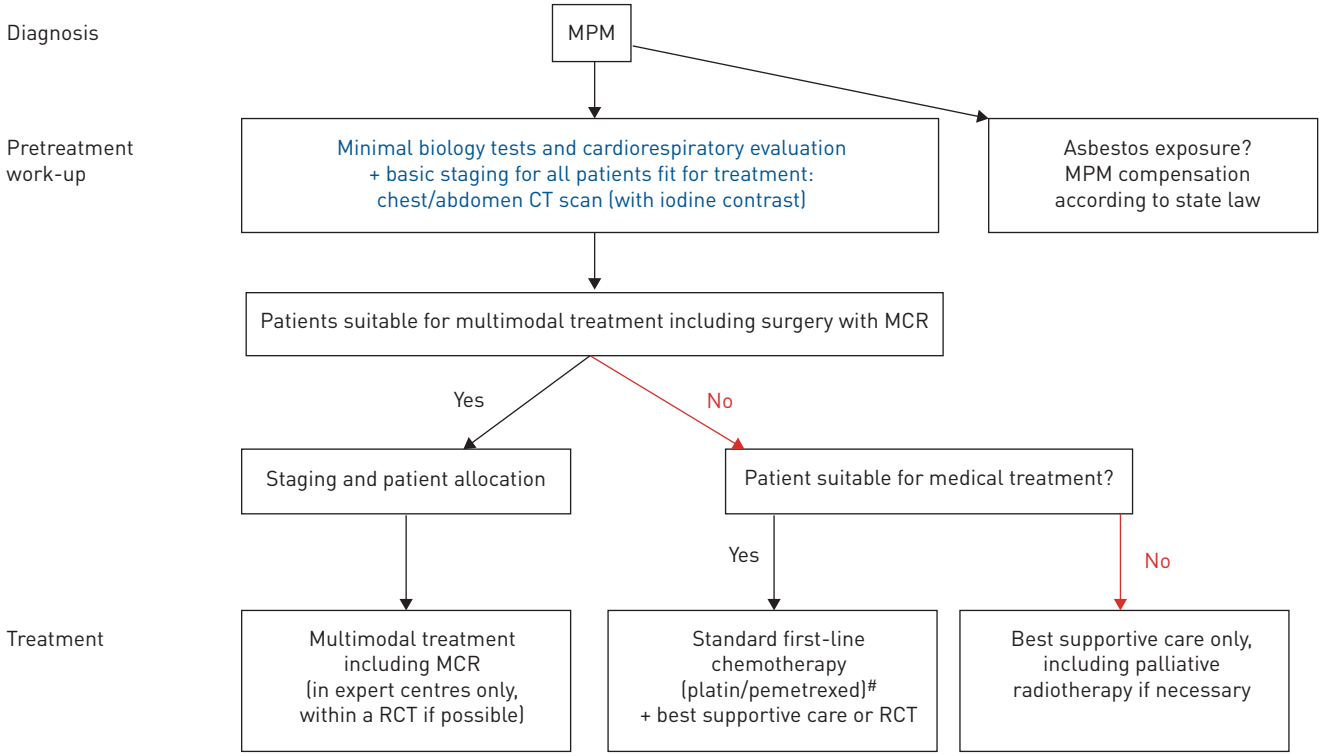

FIGURE 2 A simplified algorithm for the management of patients with malignant pleural mesothelioma (MPM). RCT: randomised controlled trial; MCR: macroscopic complete resection. #: ±bevacizumab if available and no contraindication.

Good-quality palliative care is vital for MPM patients, the majority of whom will require symptom control at some stage in the course of their disease. Currently there are no published large randomised controlled studies of symptom control in patients with MPM only. A small prospective randomised (1:1) phase II trial assessed the use of early *versus* delayed (chemo)therapy at time of symptomatic progression after best supportive care (BSC) only in 43 patients, presenting with stable symptoms after control of pleural effusion [308]. The early use of (chemo)therapy provided an extended median time to symptomatic progression *versus* the delayed (chemo)therapy group (25 *versus* 11 weeks, p=0.1), and a trend to survival advantage (median overall survival of 14 months *versus* 10 months, p=0.1).

There are a two relatively unique problems experienced by a proportion of mesothelioma patients. 1) Excessive sweating: no RCT studies have been published in this field, but it remains a common problem in a proportion of mesothelioma patients. Although there are no good-quality data, oral prednisolone can be very effective in helping to reduce this disabling symptom; 2) severe unilateral thoracic pain: a case series of 53 patients with MPM and associated persistent pain despite oral analgesia were managed with cervical cordotomy [309]. The majority of patients had a reduction in pain following the procedure; however, further, more robust studies are required to confirm this finding.

A review of the numerous palliative care intervention for patients with MPM was out of the scope of this guideline. Therefore, the task force experts encourage following existing national palliative care guidelines for guidance on pain control in cancer patients.

The task force experts emphasise that it is recognised that mesothelioma is associated with high psychological burden, and although quantitative evidence is sparse, there are qualitative papers and systematic reviews that demonstrate this [310].

Follow-up after active treatment

There are no evidence-based recommendations regarding the follow-up in mesothelioma patients undergoing a dedicated treatment mainly based on (chemo)therapy. Although (chemo)therapy has been shown to benefit patients, there are no consistent data allowing us to answer the question of the optimal duration of (chemo)therapy and the design of patients' survey after cessation of the treatment. Therefore, symptoms such as breathlessness, chest pain or both indicate re-evaluation by CT scan to search for progressive disease [308, 311, 312]. Other main symptoms consist of cough (frequently due to pleural effusion), anorexia, weight loss, fatigue, sweating, dysphagia and psychological distress. There are no data

showing the place of PET and MRI in the follow-up for MPM. The development of targeted therapies and immunotherapy in a near future would probably lead clinicians to adapt the modalities of follow-up for mesothelioma patients [313]. To date, there is no sufficient evidence for routine use of biomarkers such as blood mesothelin or other markers for follow-up of MPM patients, either to predict the response to treatment or patient outcomes.

Research priority: the role of periodic follow-up with imaging (chest/abdominal CT scan, MRI or PET) should be assessed in clinical trials.

Remarks: monitoring of disease progression should be guided by signs and symptoms occurring during clinical follow-up. However, in addition to clinical follow-up, and pending further evidence from clinical trials, the task force group suggests a chest/abdominal CT scan every 3–6 months after active treatment of MPM patients.

The outlook for MPM

After a decade during which systemic therapy for mesothelioma has languished at a therapeutic plateau [314], recent advances have demonstrated that improvement in efficacy can be associated with the addition of novel agents in the context of randomised phase III trials, *e.g.* bevacizumab [271], but not nintedanib with a negative phase III trial (NCT01907100) despite positive randomised phase II trial results [292]. The role of aggressive local control in the form of extended pleurectomy/decortication will become clearer in the next few years, but positive result of current trials may promote further discussion regarding the radicality of a surgical approach.

Despite these recent advances and awaited results from ongoing surgical clinical trials such as MARS2 (NCT02040272), a major challenge remains in the relapsed setting, where there is currently no approved standard.

Accordingly, translational and clinical research in this setting has the potential to significantly improve survival outcomes. Despite the failure of CTLA-4 checkpoint targeted immunotherapy in relapsed mesothelioma [289], the emerging signals of activity for anti-PD-1 monotherapy [295] and combination PD-1 (or PD-L1)/CTLA-4 targeted therapy [297], indicate some potential for these approaches in the relapsed and potentially frontline settings [296], as demonstrated in other cancers such as melanoma [2, 3]. However, the MAPS-2 trial reported a higher incidence of grade 3 or 4 adverse events (26.2% *versus* 12.7%), and even three toxic deaths, with the combination nivolumab/ipilimumab *versus* nivolumab alone, respectively [315]. This toxicity issue and the choice of inadequate surrogate end-points such as PFS instead of overall survival must be taken into account when assessing the value of new drugs in MPM [316].

Thus, a major challenge for the field as a whole, will be how best to predict the efficacy of both monotherapy and combination immune checkpoint inhibition. This is particularly important from a health economic standpoint to ensure that advances are ultimately affordable, as well as driving up the efficacy of therapy through enrichment of those likely to respond. Meeting this challenge will require assessment of established predictive biomarkers such as PD-L1, but also the role of other potential predictors including tumour infiltrating lymphocytes [317], cytokine expression [318] and tumour mutation burden [319, 320], ideally in the context of phase III clinical trials. Exploitation of the abscopal effect could also enhance the efficacy of immunotherapy and warrants exploration [321].

Studies are currently under development in the context of combination with both (chemo)therapy and novel agents [301] (*e.g.* focal adhesion kinase [322], bevacizumab [323]). Future advances in next-generation combination immunotherapy, *e.g.* indoleamine 2,3-dioxygenase [324]/T-cell immunoglobulin mucin-3 inhibitors [325]/vaccines, *etc.* may emerge from the rapid pace of development in basic and translational science and advances in other cancers, as well as tailoring of therapeutic hypotheses based on specific mesothelioma biology, including gene-driven metabolic reprogramming.

Genomic stratification of systemic therapy has revolutionised treatment in other areas including lung and breast cancers. Mesothelioma is lagging behind, partly due to a lack of druggable oncogenic mutations [2]. However, recent advances demonstrate potential opportunities. Arginine auxotrophy, arising from the loss of the citrulline-to-arginine converting enzyme argininosuccinyl synthetase, has recently been shown to be a druggable target [294, 326, 327] with a phase III trial now enrolling in the front-line setting. Other novel metabolic vulnerabilities may be identified from interrogation of recently available large-scale genomic data that could underpin the development of new synthetic lethal strategies.

Tumour suppressor losses are common in mesothelioma and may have implications for targeted therapy. For example, the discovery that inactivation of the BAP1 tumour suppressor is associated with upregulation of EZH2 [328] or defective homologous DNA repair [329] has led to the development of phase II trials to test this hypothesis. Other preclinical evidence suggests how sensitivity to

BOX 1 Summary of questions and recommendations

Questions	Recommendations and research priorities
Epidemiology	
MPM screening	Research priority: the relationship between pleural plaques and MPM should be ascertained in large international epidemiological studies. The effectiveness of CT screening in the asbestos-exposed population should be determined in well-designed clinical trials.
Biomarkers for MPM	Research priority: routine determination of previously proposed biomarkers in MPM have no current validated role in diagnosis, prognosis or clinical follow-up (disease monitoring). Thus, further research into the role of biomarkers in these goals is required and highly encouraged.
Staging	
Clinical staging	Research priority: prospective data collection about the measurement of tumour thickness or volume is to be encouraged.
Pre-treatment staging investigations	Research priority: the prospective use of volumetric assessment software should be encouraged.
Which other prognostic factors are of importance?	Research priority: the routine use of the Brims score is encouraged, and combined with other scores as part of clinical trials for prospective validation.
Surgery (PICO)	
Should partial pleurectomy compared to talc pleurodesis be used as a palliative procedure in patients with symptomatic MPM?	Recommendation: we recommend talc poudrage via thoracoscopy to control a recurrent MPM effusion as the first choice to achieve pleurodesis in patients with expanded lungs (strong recommendation, low quality of evidence). We suggest palliative VATS-PP to obtain pleural effusion control in symptomatic patients fit enough to undergo surgery who cannot benefit from (or after failure of) chemical pleurodesis or indwelling catheter (weak recommendation, low quality of evidence).
Should radical surgery (including extrapleural pneumonectomy or pneumonectomy/decortication) be used in patients with MPM?	Research priority: patients considered for radical surgery should be either included in prospective randomised controlled clinical trials or in national/international surgical registries. Remark: surgery may be appropriate for carefully and highly selected MPM patients. This would usually be EP/D rather than EPP, because of its lower comparative respiratory postoperative morbidity and preservation of quality of life, performed in centres of excellence and as part of multimodality treatment. Patients with sarcomatoid or sarcomatoid-predominant histology, N2 disease (8th edition TNM staging system) and/or stage IV should not be considered for radical surgery other than in the context of research. However, as no single prognostic factor influences treatment allocation, prognostic scores encompassing several prognostic factors should be preferred (see sections on staging and allocation).
Radiotherapy (PICO)	
Should radiotherapy be used for pain relief in patients with MPM?	Recommendation: we suggest that palliative radiotherapy for pain relief should be considered in cases of painful sites of disease caused by local infiltration of normal structures (moderate recommendation, low quality of evidence).
Should radiotherapy be used to prevent procedure-tract metastases (drain site parietal seeding) in patients with MPM?	Recommendation: we do not recommend prophylactic drain site radiotherapy in routine clinical care (strong recommendation, moderate quality of evidence).
Should adjuvant post-operative radiotherapy be used in patients with MPM?	Research priority: radiotherapy after pleurectomy±decortication or after EPP should only be considered within the context of clinical trials and/or included in national/international surgical registries.
Medical treatment (PICO)	
Should first line chemotherapy consisting of platinum in combination with pemetrexed be used in patients with MPM?	We recommend first-line combination (chemo)therapy consisting of platinum and pemetrexed (with folic acid and vitamin B12 supplementation) in patients fit for (chemo)therapy (good performance status, ECOG performance status 0–2, no contraindications) (strong recommendation, low quality of evidence). Research priority: patients demonstrating prolonged symptomatic and objective response with first-line pemetrexed-based (chemo)therapy may be treated again with the same regimen in the event of recurrence. In the remainder of cases, inclusion of the patients in clinical trials is highly encouraged.
Should targeted therapies be added to first line standard chemotherapy in patients with MPM? Should bevacizumab be added to first line standard chemotherapy in patients with MPM?	Recommendation: we suggest that bevacizumab, if available, be proposed in combination with cisplatin/pemetrexed as first-line treatment in patients fit for bevazucimab and cisplatin, but not for macroscopic complete resection (weak recommendation, moderate quality of evidence).

Continued

BOX 1 Continued

Questions	Recommendations and research priorities
Should immunotherapy be used as salvage therapy in patients with MPM who failed first-line standard chemotherapy?	Research priority: novel insights in immunotherapy are promising, but need further development and results from ongoing or planned phase III trials before any definitive recommendations can be made for their use in the clinical routine. Inclusion of patients in these trials is highly recommended.
Multimodal treatment (PICO)	
Should a multimodal therapy approach (combining more than one method of cancer treatment: surgery, chemotherapy, radiation therapy) compared to chemotherapy alone be used in patients with MPM?	Research priority: we still recommend that patients who are considered candidates for a multimodal approach should be adequately informed of its challenges and referred to expert centres in order to be included in a prospective (randomised) clinical trial or registered in a large institutional database.
Treatment allocation of MPM	Research priority: current and future scores suggested for patient treatment allocation, always decided by an MPM expert multidisciplinary board, would require prospective validation by multicentre studies.
Follow-up of MPM patients	
What should be the follow-up of a patient after active treatment of MPM?	Research priority: the role of periodic follow-up with imaging (chest/abdominal CT scan, MRI or PET) should be assessed in clinical trials. Remarks: monitoring of disease progression should be guided by signs and symptoms occurring during clinical follow-up. However, in addition to clinical follow-up, and pending further evidence from clinical trials, the task force group suggests a chest/abdominal CT scan every 3–6 months after active treatment of MPM patients.

chemotherapeutic agents can be BAP1-driven and prompt a future patient stratification to improve the efficacy of standard treatments [330]. Emerging insights into other synthetic lethal interactions with CDKN2A and NF2 have significant translational potential.

Micro-RNAs (MiRs) broadly regulate the transcriptome of mesothelioma and may contribute to the drug-resistant and aggressive phenotype. Recently, MiR16 has been identified as a potential tumour suppressor that can be targeted using so-called targoMiRs. Van Zandwijk *et al.* [331] reported that MiR-directed targoMiR can be delivered in the clinical setting and can induce responses in relapsed mesothelioma, suggesting that this approach could have therapeutic potential in the future.

The apparently unique treatment-resistant profile of mesothelioma prompts a need for in-depth preclinical research to gain an increased understanding of mesothelioma biology. Potential areas of focus for research include microenvironment–tumour interaction, gene-driven metabolism [329, 332] and elucidation of the mechanisms behind cell death. Preclinical research should use accurate models such as organoids, patient-derived xenografts, primary cells and fresh tissues, and humanised mouse models to study immune response. Ultimately, randomised clinical trials for prospective therapies should use strong primary end-points such as overall survival comparing outcomes to the current standard therapies. At the clinical level, patients should be stratified based on strong data from genetic and cell biological preclinical analysis of mesothelioma cells.

The awareness of these gaps along with the increasing pace of knowledge regarding genomics and biology of mesothelioma will allow to multiply our chances of achieving a real improvement of the clinical outcomes for patients.

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The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

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Table S1: Summary of recent reviewed studies related to age-standardized incidence/mortality rates of malignant mesothelioma

part 1a-Word publications (2010-2017)

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Bianchi et al. 2014 [10]	World		Different sources		Standard World population 2000	Countries at high incidence (> 2 among men) : UK, Australia, Netherlands, New Zealand, Belgium, Republic of Malta Countries with intermediate incidence rates (>1-2) : Denmark, Finland, Norway, Sweden, Iceland, Germany, France, Italy, Croatia, Austria, Cyprus, United States, Israel, South Africa Countries with low incidence rates (<1) or insufficient data : Central Europe, Spain, Ireland, Japan, Lebanon, Jordan, China, South Korea, Taiwan, Hong Kong, Singapore, India, Thailand, Middle East
Delgermaa et al. 2011 [11]	World	1994-2008	World Health Organization Mortality Database		Standard World population 2000	Mortality rate Overall : 0.49 Men : 0.9 Women : 0.19 US : 0.5 UK and northern Ireland : 1.78 Japan : 3.2 Germany : 0.68 France : 0.76 Netherlands: 0.64 Australia: 1.65 Italy: 1.03 South Africa: 0.67 Spain: 0.39

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Kameda et al 2014 [14]	World	1994-2012	World Health Organization Mortality Database and searched PubMed or governmental websites	ICD-9 ICD-10 C45	Standard World population 2000	Countries with early asbestos ban = 0.94 Countries with late asbestos ban = 0.37 Countries with no asbestos ban = 0.32 All = 0.78
Odgerel et al. 2017 [12]	World	1994-2014	WHO Mortality Database	C45	Standard World population 2000	Crude mortality rate for 104 countries : from 0.004(in Egypt) to 4.456(in the British Virgin Islands) Mean and median of mortality rates: 0.660 and 0.291
Soberg et al. 2015 [15]	World	2003-2007	10th volume of the Cancer Incidence in Five Continents (IARC)	ICD-10 C45	SegiWorld population	Countries with a age-standardized incidence rate among men > 2.0 : Australia (all jurisdictions), Belgium, England, France (1 out of 11 jurisdictions reported), Germany (4 out of 9 jurisdictions reported), Italy(8 out of 33 jurisdictions reported), New Zealand, The Netherlands, Northern Ireland, Scotland, Switzerland (3 outof 9 jurisdictions reported), and Wales
Le et al. 2011 [16]	World	1994-2008	WHO Mortality Database	ICD-10 C45	Standard World population 2000	Age adjusted mortality rate highest for Cyprus (0.479), Israel(0.367) and Japan (0.325) Japan : linear increase of mesothelioma mortality since 1995 (peak use of asbestos : 1970-1990) Korea : increase in mesothelioma mortality that has slowly risen since 1995 (peak use of asbestos : 1975-1995) Singapore : sharp increase since 1995 (peak use of asbestos : 1975)

Table S1: Summary of recent reviewed studies related to age-standardized incidence/mortality rates of malignant mesothelioma

Part 1b-countries reporting age-standardized incidence/mortality rates over 2/100,000 among men (2010-2017)

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Fazzo et al. 2012 [17]	Italy	1995-2002	Death certificates	ICD-9 code 163	Standard Italian population 2001	0-39 years men : 0.04 [0.03-0.05] women : 0.03 [0.02-0.05] 40-75 years men : 4.91 [4.71-5.11] women : 1.71 [1.60-1.82] 76-99 years men : 16.37 [15.61-17.15] women : 5.56 [5.23-5.90]
Marinaccio et al. 2012 [18]	Italy	1993-2004	Italian National Mesothelioma Register (ReNaM)		Standard Italian population 2001	Men : 3.49 Women : 1.25
Korda et al. 2016 [19]	Australia	1994-2011	Australian Capital Territory (ACT) Cancer Registry (1982- 2014) Western Australia (WA) Cancer Registry Australian Cancer Database (1982-2011)	ICD-O-3	Standard Australian population	both sexes (crude rates) ACT 2009-2011 : 2.95 (2.02-4.17) Rest of Australia 2009-2011 : 2.94 (2.80-3.08) Rates increased 12% more in ACT than the rest of Australia Rose of incidence in ACT at least up to 2009-2011

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Soeberg et al. 2016 [20]	Australia	1972-2009	New south wales cancer registry	ICD-10C45 ICD-O-3	Australian 2001 World standard population Segi population	Australian standardization 2009 : 2.6 (95%CI 2.3–3.0), men : 4.8 (95%CI 4.1–5.5) / women : 0.8 (95%CI 0.5–1.0) 1994 : highestage-standardized incidence rate for men:5.7 (95%CI 4.7–6.6) 2003 : highest age standardizedincidence rate for women : 1.1 (95%CI: 0.7–1.4)
Soeberg et al. 2016 [21]	Australia	1982-2009	Population-based Australian Cancer database	ICD-10 C45 ICD-O-3	Australian 2001 standard population SegiWorld population	Men : 2.1 in 1982 Average percent of change (APC) : +3.4 (2.5-4.4) 1982-1994 : +6.8 (4.8-8.8) 1994-2009 : 0.8 (-0.1-1.7) Women : 0.3 APC : +4.9 (3.6-6.2) 1982-1994 : +6.7 (5.3-8.1) 1994-2009 : -0.2 (-3.5-3.3) peaked during 2005–2010 for MPM aged 65-74 years peak around 2020 for MPM aged 75 years or more

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Krupoves et al. 2015 [22]	Quebec Canada	2008-2034	Canadian cancer registry	1992-2007ICD-O-3C38.4+M905C38.8+M9051984-1991ICD9 code 163+ ICD-O M905	Standard Quebec population 1996	Quebec Men : 2.12 Women : 0.42 Average annual rate of change Men 1984-2007 : +2.71% per year (+1.75-+3.67) 1984-1995 : +6.41 (+3.66-+9.22) 1996-2007 : +0.65 (-1.47-+2.81) Women 1984-2007 : +2.60 (+1.02-+4.20) 1984-1995 : +3.55 (-1.46-+8.82) 1996-2007 : -0.92 (-4.45-2.74) Rest of Canada Men : 1.46 Women : 0.21 Average annual rate of change Men 1984-2007 : +2.00 (+1.19-+2.81) 1984-1995 : +3,06 (+1.31-+4.83) 1996-2007 : +0.33 (-1.42-+2.10) Women 1984-2007 : +2.53 (+1.13-+3.96) 1984-1995 : +0.14 (-4.22+4.70) 1996-2007 :+2.84 (-0.45-+6.24)

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Van den Borre et al. 2014 [23]	Belgium	1994-2008	Death certificates WHO mortality database	ICD-8code 163.0 ICD-9code 163ICD-10C45	Standard World population 2000	0.96 Men: increased from 0.25 to 2.63 over the 40-year periods Increased annual rate of +6.65% Since 1983 : +5.44% Women increased from 0.16 to 0.41 over the 40-year period Increased annual rate of +3.04% Since 1983 : +2.80%
Tomasson et al. 2016 [24]	Iceland	1965-2014	Population-based Icelandic Cancer Registry National Cause of Death Registry National Register	ICD-10 C45 ICD-O-3 9050/3 9051/3 9052/3 9053/3	-	Men 1965-1974 : 0.14 (0.01-0.71) 1975-1984 : 0.48 (0.15-1.16) 1985-1994 : 0.94 (0.46-1.72) 1995-2004 : 1.76 (1.09-2.69) 2005-2014 : 2.14 (1.44-3.07) Women 1965-1974 : 0.29 (0.05-0.96) 1975-1984 : - 1985-1994 : 0.31 (0.08-0.85) 1995-2004 : 0.37 (0.12-0.88) 2005-2014 : 0.56 (0.24-1.10)

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Schonfeld et al. 2014 [25]	Germany	2000-2010	Death certificates WHO mortality database	ICD-10 C45	Standard European population truncated to the age of 40 years and older (ASR40+)	2000-2010 Men : 3.9 East Germany : 1.7 annual percent of change <65 yrs : -4.0 (-8.2-0.5) annual percent of change 65+ yrs : 1.0 (-1.7-3.7) West Germany : 4.6 annual percent of change <65 yrs : -5.5 (-6.8--4.3) annual percent of change 65+ yrs : 2.9 (2.1-3.7) Women : 0.8 East Germany : 0.6 annual percent of change <65 yrs : -2.5 (-9.2-4.6) annual percent of change 65+ yrs : -0.3 (-3.9-3.4) West Germany : 0.9 annual percent of change <65 yrs : -2.8 (-5.4--0.1) annual percent of change 65+ yrs : -0.1 (-1.6-1.3) predicted peak in both regions around 2020

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Lehnert et al. 2017 [26]	Germany	2009-2013	Population-based cancer registry	ICD-10 C45	Standard European population truncated to the age of 40 years and older (ASR40+) - Standard European population (EuPop) - World Segi - Standard world population 2000	ASR40+ Men : 4.78 (4.64;4.90) Women : 0.98 (0.92-1.04) EuPop Men : 2.06 (2.00-2.12) Women : 0.43 (0.41-0.46) World Segi Men : 1.33 (1.30-1.37) Women : 0.29 (0.28-0.31) World WHO Men : 1.56 (1.52-1.60) Women : 0.33 (0.32-0.35) Significant downward slopes in men of -0.67 (95% CI -1.10; -0.24) for Bremen and -0.57 (95% CI -0.88;-0.26) for Hamburg, but not for the other federal states Annual rates for women varied without a clear trend
Zadnik et al. 2017 [27]	Slovenia	1961-2014	Cancer Registry of Slovenia	ICD-10	Segi World population	2005-2009 (Men and women): 1.5 Male: 2.3 1998-2003: increased incidence : +13.5% (95%CI: 5.7-20.6) After 2004: -0.4% (-5.1- -3.9)

Table S1: Summary of recent reviewed studies related to age-standardized incidence/mortality rates of malignant mesothelioma:

Part 1c- countries reporting age-standardized incidence/mortality ratesbetween 1/100,000 and 2/100,000 among men (2010-2017)

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Glynn et al. 2017 [28]	United-States	1973-2012	SEER registries	ICD-10Code C45/C38.4	Standard US population 2000	Men Urban: 1.72 increase of incidence rates by 4.16% (95% CI: 3.01, 5.31) per year from 1973 to 1992 and decrease by 1.89% (95% CI: –2.60,–1.17) per year after 1992 Rural: 0.2 increase of incidence rates by 23.8%(95% CI: 7.28, 42.8) per year from 1973 to 1980 and constant annual incidence rate through 2012 Women Urban: 1.14 increase of incidence rate by 2.82% (95% CI: 1.34, 4.32) per year from 1973-1993 and constant annual incidence rate through 2012 Rural: 0.265 Stable trend from 1973-2012: 1.05%; 95% CI: –0.0189, 2.14)
Henley et al. 2013 [29]	United-States	2003-2008	National Program for Cancer Registries and the Surveillance, Epidemiology, and End Results registries	ICD-O C38.4 C48 Other mesothelioma	Standard US population 2000	2003-2008 : 1.05 (95% CI: 1.03–1.06) Men : 1.93 (95% CI: 1.90-1.97) Decrease of incidence rate by 2.6% Women : 0.41 (95%CI: 0.41-0.43) Stability of incidence rate State rates from 0.58 to 1.65

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Mokdad et al. 2017 [30]	United-States	1980-2014	National Center for Health Statistics (NCHS) Human Mortality Database	Global Burden of Diseases, Injuries, and Risk Factors Study (GBD)	Standard US population 2000	1.0
Helland et al. 2012 [31]	Norway	1970-2009	Cancer Registry of Norway		Standard World population 2000	Men Rates in 1970-1974 : 0.3 Rates in 2000-2004 : 1.6 Rates in 2005-2009 : 1.5 Age-adjusted annual increase : 4.2% Women Rates in 1970-1974 : 0.1 Rates in 2000-2004 : 0.2 Rates in 2005-2009 : 0.3 Age-adjusted annual increase : 2.9%
Kielkowski et al. 2011 [32]	South Africa	1995-2007	Death certificate	ICD-9code 509 (Own code of Stats SA) ICD-10code C45	Standard World population 2000	Men 1995 : 1.5 (1.2-1.7) 2000 : 1.1 (0.9-1.3) 2005 : 1.2 (1.0-1.4) 2007 : 1.3 (1.1-1.5) No statistically significant trend Women 1995 : 0.4 (0.3-0.5) 2000 : 0.4 (0.3-0.5) 2005 : 0.3 (0.2-0.3) 2007 : 0.3 (0.3-0.5) No statistically significant trend

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Jennings et al. 2014 [33]	Ireland	1994-2009	National Cancer Registry of Ireland		Standard European population	Men 1994-1997 : 0.908 1998-2001 : 0.802 2002-2005 : 1.235 2006-2009 : 1.311 1994-2009 : 1.064 Women 1994-1997 : 0.089 1998-2001 : 0.205 2002-2005 : 0.133 2006-2009 : 0.136 1994-2009 : 0.141

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Le Stang et al. 2010 [34]	France	1980-2003	National French mesothelioma surveillance program	ICD-O-3C38.4	Standard World population 2000	Men FRANCIM 1980 : 0.8 1990 : 1.3 2000 : 1.4 2005 : 1.2 Evolution rate1980-2005 : 1.7 2000-2005 : 3.4 PNSM 1998 : 1.11 2005 : 0.93 Slight falling trend Women FRANCIM 1980 : 0.2 1990 : 0.3 2000 : 0.3 2005 : 0.4 Evolution rate 1980-2005 : 3.1 2000-2005 : 1.8 PNSM 1998 : 0.18 2005 : 0.29
Skammeritz et al. 2013 [35]	Denmark	1943-2009	Danish Cancer Registry	ICD-7 ICD-10 ICD-O-3	Standard World population 2000	Men Increase of incidence over the period 2008-2009 : 1.76 Women Steady incidence since 1990 around 0.3

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Järvholm et al. 2015 [36]	Sweden	1995-2013	National Swedish Cancer Registry	ICD-7 1622 histo : Code 776	Standard Swedish population 2000	Men Decrease of age-adjusted incidence rate: -1.3% Women No clear trend of age-adjusted incidence rate: +0.6%
Zhao et al. 2017 [37]	China		National central cancer registry	ICD-10 C45	Segi World population	2013 Male: 1.19 Female: 0.87 2000-2012 Male: 0.2 (95% CI: -2.5-2.9) Female: -1.8 (95 %CI: -3.5-0.0)

Table S1: Summary of recent reviewed studies related to age-standardized incidence/mortality rates of malignant mesothelioma

Part 1d- countries reporting age-standardized incidence/mortality rates under 1/100,000 among men (2010-2017)

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Algranti et al. 2015 [38]	Brazil	2000-2012	Death certificates	ICD-10Code C45/C38.4	Standard Brazilian population 2010	C45 Brazil : 0.07-0.1 No significant trend São Paulo : 0.1-0.21 Significant linear trend C38.4 Brazil : 0.1-0.16 No significant trend São Paulo :0.08-0.19 No significant trend Incidence peak around 2021-2026
Jung et al. 2012 [39]	Korea	2001-2010	Korean mesothelioma surveillance system		-	2001 : 0.027 2005 : 0.075 2008 : 0.125 2010 : 0.087 Gender ratio over the decade : 1.96
Kwak et al. 2017 [40]	South Korea	1994-2013	Korea Central Cancer Registry (KCCR)	ICD-10 C45	Standard World population 2000	Men 2009-2013 : 0.228 Increase continuously and slowly until 2019±2023 Women 2009-2013 : 0.113 Increase continuously and slowly until 2019±2023

Author	Country	Study period	Data	Classification	Standardization	Age-adjusted incidence (mortality) rate / 100,000
Lee et al. 2010 [41]	Taiwan	1979-2005	Population-based Taiwan Cancer Registry	ICD-0 Codes 163 and 158 9050/3, 9051/3, 9053/3	Standard World population 2000	Increased age-standardized incidence rate over the period 1979-2005 Men - 2005 : approximatively 0.16 Women - 2005 : approximatively 0.1
Tse et al. 2010 [42]	Hong-Kong	?	Hong Kong cancer registry	ICD-10 C45	World standard population 1966	Men Before 1993–1994, the moving average of ASIRs : 0.016–0.073 1993–1994 : 0.125–0.156 peak in 2004 : 0.386 2006: 0. 347 (slight decrease) Women Similar trend until 1992 Incidence stable since 1994, may be a slight decrease
López-Abente et al. 2013 [43]	Spain	1976-2010	Death certificates	ICD-9Code 163ICD-10C38,4, C45,0	European Standard population	Men 1976-1980 : 0.347 1991-1995 : 0.566 2006-10 : 0.644 levelling-off from the period 2001–2005 Prediction for 2011-15: 0.620 Prediction for 2016-20: 0.577 Women 1976-1980 : 0.233 1991-1995 : 0.219 2006-10 : 0.196 gradual decline from the 1980s Prediction for 2011-15: 0.177 Prediction for 2016-20: 0.163

Table S2: Summary of recent reviewed studies related to population attributable risk of asbestos exposure for malignant mesothelioma (2010-2017).

Authors	Country	Period	Exposure	Design	Cases enrolment	Controls enrolment	Diagnostic	Questionnaire	Exposure assessment	Population attributable fraction
Aguilar-Madrid et al 2010 [49]	Mexico	2004-2006	Occupational exposure	Hospital-based case-control study	Insured workers with suspected diagnosis MPM n=119	Hospital controls randomly selected from the insured-worker population data Frequency-matched on sex, age (+/- 5 years), insurance type and geographical area n=353	Immuno-histopathology confirmed	Standardized questionnaire Face to face interviews	Expertise certain/likely/possible	44%
Rushton et al 2010 [50]	UK	2005	Occupational exposure	Cross-sectional	National data sources: Carcinogen Exposure database UK labour force survey Census employment UK mesothelioma studies		ICD-10 C45		CAREX	Men: 97.0% Women: 82.5%

Authors	Country	Period	Exposure	Design	Cases enrolment	Controls enrolment	Diagnostic	Questionnaire	Exposure assessment	Population attributable fraction
Lacourt et al 2014 [51]	France	1998-2002	Occupational and non-occupational exposure	Population based case-control study	Incident cases identified through the PNSM n=437 (362 men and 75 women)	General population, 2 controls/case Matched on sex, age (±5 years) and district of residence. N= 874 (724 men, 150 women)	Certified by a standardised diagnostic confirmation procedure	Standardized questionnaire Face-to-face interviews	Expertise Not exposed/ Possible/ Probable Cumulative exposure index (f/ml-yrs) : <0,1/ 0,1-1/ 1-10 / >10 Occupational only/ Non occupational only/ both	Occupational exposure: Men: 83.1% Women: 41.7% Non-occupational exposure: Men: 20.0%Women: 38.7% All exposure: Men: 87.3% Women: 64.8%
Ferrante et al 2016 [52]	Italy	2001-2006	Occupational and non-occupational exposure	Population-based case-control study	Incident cases identifiedin different units of the hospitals serving the study area n=223	General population Matched by date of birth (±18 months) and gender n=552	Histological and/or cytological confirmation	Standardized questionnaire Face-to-face interviews	Expertise Cumulative exposure index : background level (<0,1)/ 0,1-1/ 1-10 / >10	All subjects : 89.4% Non-occupationally exposed only : 82.1%

Table S3: Summary of recent reviewed studies related to the relationship between non-occupational asbestos exposure and pleural mesothelioma (2010-2017).

Author	Country	Exposure type	Design	Period	Study population	Data Sources	Exposure assessment	Results
Baumann et al 2011 [55]	New Caledonia	Natural sources of asbestos	Cluster and ecological study	1984-2008	Histologically confirmed cases (n=109) Comparison of 100 tribes: tribes with MM cases (n = 34) and without MM cases (n = 48).	Cancer Registry of New Caledonia ; Questionnaire: cases or two of their closest relatives	self-report Identification and characterization of sources of natural asbestos	Age-standardized incidence: Noumea: 0.64 (95% CI: 0.13-1.88) Houaïlou: 128.66 (95% CI: 70.41-137.84) Koné: 25.46 (95% CI: 14.25-41.98) Poindimié: 15.37 (95% CI: 3.17-44.92) Identification of a spatial cluster grouping 18 tribes (31 observed cases vs 8 expected Serpentine on roads : OR=13.0 (95% CI: 10.2-16.6) Increased risk with serpentine surface, proximity to serpentine quarries, and distance to the peridotite massif No significant association with whitewash
Berk et al 2014 [56]	Turkey	Environmental exposure	Case series	1993-2010	Confirmed cases diagnosed in Sivas (n=219, 126 men, 93 women)	Hospital records	Rock, soil and house plaster samples	Male:female ratio: 1.4:1 1.8 % patients with an occupational history with a potential risk for asbestos exposure 86 % patients with a history of living in a house containing asbestos-contaminated soil

Author	Country	Exposure type	Design	Period	Study population	Data Sources	Exposure assessment	Results
Bourgault et al 2014 [57]	Quebec	Environmental exposure			General population of Thetford Mines	Mortality data from the Ministry of Health and Social Services of the Province of Quebec, covering the 2000–2003 period Potency factors calculated by Berman and Crump for the Quebec mining and milling cohort	Indoor and outdoor measurements lifetime exposure concentration: sum of the average indoor and outdoor exposures concentrations, weighted by the respective proportion of the time spent indoors and outdoors	Lifetime mortality risk (/100000) from environmental exposure to asbestos fibers in Thetford Mines : 0.7-2.3 Health's Canada threshold for considering a lifetime cancer risk as negligible: 1/100 000
Corfiati et al 2015 [58]	Italy	All types	Population-based case series	1993-2008	Histologically confirmed cases (n=15322)	Italian national mesothelioma registry (ReNaM) Interviews	Expertise: - Occupational: definite, probable, possible -Familial -Environmental -Other non-occupational	Identification of 32 clusters mostly located in southern Italy Main source of asbestos exposure : asbestos cement manufacturing industries, shipbuilding and repair facilities Cases for which environmental exposure was ascertained are mostly concentrated in clusters where asbestos cement plants were located

Author	Country	Exposure type	Design	Period	Study population	Data Sources	Exposure assessment	Results
D'Agostin et al 2017 [59]	Italy	Para-occupational	Population-based case series	1995-2014	Histologically confirmed mesothelioma cases (n=1063)	Friuli Venezia Giulia Mesothelioma Register Interview	Self-report and expertise	Para-occupational exposure : 35 cases (33 women and 2 men)
Driece et al 2010 [60]	Netherlands	Environmental exposure (asbestos pollution of friable and non-friable waste products)	Ecological study	1960–2007	Resident of municipality Hof van Twente	Demographic and mortality databases	Number and size of polluted sites per postal code Number of exposed households per postal code Historical measurements	416 sites with asbestos pollution were identified High exposure category - Site approach: 78 extra cases - maximum : 431 cases during the 48-year period with asbestos contamination in the region - Household approach: 42 extra cases - maximum : 231 cases Intermediate exposure category - Site approach: 2.8 extra cases - maximum : 15.4 cases - Household approach: 1.7 extra cases - maximum: 9.1 cases Low exposure category - Site approach: 3.1 extra cases - maximum : 16.9 cases - Household approach: 1.5 extra cases - maximum : 8.0 cases

Author	Country	Exposure type	Design	Period	Study population	Data Sources	Exposure assessment	Results
Fazzo et al 2014 [61]	Italy	Environmental exposure (asbestos-cement plant)	Ecological study	2001-2007	Residents of Coroglio-Bagnoli in Naples (n= 174682; 132 881 in subarea 1 and 41 801 in subarea 2)	Demographic database Italian national mesothelioma registry (ReNaM)	SIG Expertise and company records	34 men and 12 women cases Study area vs Campania Region SIR=2.30 95%CI : 1.59-3.21 for men SIR=2.26 95%CI : 1.17-3.95 for women subjects non occupationally exposure to asbestos Men (n=19) : SIR = 2.48; 95% CI: 1.49-3.88 Women (n=11) SIR = 1.34; 95% CI: 0.67-2.40
Ferrante et al. 2016 [52]	Italy	Occupational and non-occupational exposure	Case-control	2001-2006	223 confirmed cases 552 Controls were randomly selected from the population rosters of the LHA of Casale Monferrato	Standardized questionnaire administered face-to-face by trained interviewers	Expertise	Subjects non-occupationally exposed Background level : OR=1 >=0.1-1 : OR=3.8 (95%CI:1.3-11.1) >=1-10: OR= 14.8 (95%CI:5.7-38.6) >=10: OR=23.3 (95%CI:2.9-186.9) Having an exposed family members: OR=2.4 (95%CI: 1.3-4.4)

Author	Country	Exposure type	Design	Period	Study population	Data Sources	Exposure assessment	Results
Gogali et al 2012 [62]	Greece	Domestic exposure (tremolite-containing whitewash)	cohort	1980-2009	Residents of Metsovo municipality (n=4,417) Histologically confirmed cases (n=26)	Hospital and medical records Death certificates	no history of asbestos-related occupation or radiation treatment	Cumulative incident rate 1980-2009: 2.04/10 000 person-yrs Analyses by 15 years intervals (no statistical difference) 1980-1994: 2.2/10 000 person-yrs 1994-2009: 1.8/1 0000 person-yrs Analyses by decades 1980-1989: 2.6/10 000 person-yrs 1990-1999: 2.4/10 000 person-yrs 2000-2009: 1.1/10 000 person-yrs Metsovo population: 2.04/10 000 person-yrs Loannina population outside Metsovo: 1.48 per 1,000,000 person-yrs Abandonment of tremolite-containing whitewash associated with a drop of mesothelioma incidence

Author	Country	Exposure type	Design	Period	Study population	Data Sources	Exposure assessment	Results
Goldberg et al 2010 [63]	France	All types	Population-based case series	1998-2008	Histologically confirmed cases residents of 26 French geographical districts (n=1937 ; 21.2% women)	Death certificates National Mesothelioma Surveillance Program	Questionnaire and expertise (occupational and non-occupational)	Mortality rates spatially heterogeneous 0.84-5.08 per 100 000 men 0.11-1.62 per 100 000 women Correlations between men and women SMRs r=0.76 (95% CI 0.31 to 0.84) Correlation between men and women SIRs r=0.80 (95% CI: 0.49-0.87) Burdenof environmental asbestos exposure in industrialized countries non negligible
Goswami et al 2013 [64]		Domestic exposure	Meta-analyses	1960-2012	Published literature related to domestic exposure 12 cohort and case-control studies			Summary relative risks estimates Overall= 5.02 (95% CI: 2.48-10.13) Case control studies without occupational exposure=3.11 (95% CI: 1.64-5.9)
Lacourt et al 2014 [51]	France	Occupational and non-occupational exposure	Case-control	1998-2002	437 confirmed cases identified through the PNSM 874 controls, selected from the general population, were matched with cases for sex, age (±5 years) and district of residence.	Questionnaire	Expertise	Among subjects non-occupationally exposed to asbestos (9 male and 36 female cases / 18 male and 72 female controls) OR for non-occupational asbestos exposure Men: 2.4 (95% CI: 0.2-26.7) Women: 4.3 (95% CI: 1.2-15.1)

Author	Country	Exposure type	Design	Period	Study population	Data Sources	Exposure assessment	Results
Langhoffet al 2014 [65]	Denmark	Para-occupational	Case series	1996-2012	Histologically confirmed female cases diagnosed at Aalborg University hospital (n=24)	Hospital records	Expertise	Domestic exposure identified in 46% (11/24) of cases through their husbands or sons
Lopez-Abente et al 2012 [66]	Spain	Environmental exposure (Industrial pollution)	Ecological study	1997-2006	Residents of 8,098 Spanish municipalities	Demographic and mortality databases	SIG	Populations residing ≤2 km from pollutant facilities faced a higher risk than did unexposed or distant populations Statistically significant RRs in both sexes in the vicinity of 7 of the 24 industrial groups studied (RR, 95% CI) - biocide facilities (2.595, 1.459–4.621) - ship-building (2.321, 1.379–3.918) - glass and mineral fiber production (1.667, 1.041–2.665) - non-hazardous waste treatment (1.737, 1.077–2.799) - galvanizing (1.637, 1.139–2.347) - organic chemical plants (1.386, 1.075–1.782) - food and beverage sector (1.255, 1.006–1.562)

Author	Country	Exposure type	Design	Period	Study population	Data Sources	Exposure assessment	Results
Marinaccio et al 2015 [67]	Italy	Non-occupational asbestos exposure	Population-based case series	1993-2008	Histologically confirmed cases (n=15845)	Italian national mesothelioma registry (ReNaM) Questionnaire	Expertise	15 845 cases of MM were identified SIR in 2008 Men: 3.84 cases per 100 000 inhabitants Women: 1.45 cases per 100 000 inhabitants Proportion of MM cases due to non-occupational asbestos exposure (familial, environmental or related to leisure activities) : 10.3% Female/male ratio - population with non-occupational exposure: 2.3:1 - population with familial modalities of exposure 5.9:1 Clusters of cases due to environmental exposure: - asbestos-cement industry plants (Casale Monferrato, Broni, Bari) - shipbuilding and repair activities (Monfalcone, Trieste, La Spezia, Genova) - soil contamination (Biancavilla in Sicily)

Author	Country	Exposure type	Design	Period	Study population	Data Sources	Exposure assessment	Results
Mensi et al 2015 [68]	Italy	Occupational Para-occupational Environmental	Population-based case series	2000-2011	Histologically confirmed cases living in Lombardy (n=147)	Lombardy Mesothelioma Registry Questionnaire	Self-report and expertise	147 MM cases versus 17.45 expected Past-occupational asbestos exposure at the asbestos cement factory : 38 cases (2.33 expected), 32 were men 6 women In Family of Broni factory workers: 37 cases (4.23 expected), 5 men and 32 women Residents of Broni or adjacent towns: 72 cases (10.89 expected) 23 men and 49 women
Mirabelli et al 2010 [69]	Italy	Para-occupational Environmental	Population-based case series	1993-2001	Histologically confirmed cases n=(3746 men, n=1427 women)	Italian national mesothelioma registry (ReNaM) Questionnaire	SIG and Expertise (available for 3352 cases)	294 cases without occupational exposure (8.3%) and : - environmental exposure (living in the vicinity of industrial or natural sources) : 144 cases - para-occupational exposure : 150 cases Women: 51% of all cases with environmental exposure and 84% of those with familial exposure.

Author	Country	Exposure type	Design	Period	Study population	Data Sources	Exposure assessment	Results
Olsen et al 2011 [70]	Australia	Home renovation	Population-based case series	1960-2008	Confirmed cases diagnosed in western Australia (n=1631, 1408 men, 223 women)	Western Australia mesothelioma register Questionnaire Medical records	Expertise	Occupational asbestos exposure : 82.8% of male cases / 16.6% of female cases 195 cases associated with non-occupational exposure (6.8% of male cases and 44.4% of female cases) Between 2005-2008 : 8.4% of male cases and 35.7% of female cases attributed to home renovation
Reid et al 2013 [71]	Australia	Environmental exposure (living in an asbestos mining town)	Cohort	1950-2007	former residents' cohort of Wittenoom who had lived in the town but who had not worked for the asbestos company (4,768 people ; 2,608 females)	Cancer registries Death certificates Demographic registry	Outdoor historical measurement	Women who first arrived at Wittenoom aged <15 years (n=13) SIR=70.05 (95% CI 36.20-122.37) SMR =75.6 (95% CI: 34.6–143.6) Men who first arrived at Wittenoom aged <15 years (n=29) SIR=44.54 (295% CI 9.83-63.98) SMR= 56.5 (95% CI: 35.8–84.8) No consistent trend on MM for age of arrival at Wittenoom Exposure to blue asbestos in childhood is associated with an increased risk of mesothelioma in adults

Author	Country	Exposure type	Design	Period	Study population	Data Sources	Exposure assessment	Results
Salerno et al 2013 [72]	Italy	Environmental exposure (near an oil refinery plant)	Cohort	2003-2009	All residents in Cerano during the time period 2003-2009	Piedmont Region database Hospital records		4 cases in women, 2 in men women SIR = 9.09; (95%CI:6.13-12.0) with the district of the Local Health Authority of Novara population SIR =7.01; (95%CI: 4.41-9.60) with population in Turin men : SIR = 1.11; (95%CI: 0.0-2.57) with the district of the Local Health Authority of Novara population SIR =2.17; (95%CI: 0.13-4.21) with population in Turin RR=2.32 (95%CI: 0.04-3.98) among born/resident in Cerano and residents not born in Cerano
Tarrés et al 2013 [73]	Spain	Environmental exposure (industrial source of asbestos)	Cohort	2000-2009	Histologically confirmed cases who had been living in the area around an asbestos cement plant in the province of Barcelona for some time while the plant was functioning (1907–1997) and up to the time of the diagnosis	medical records	SIG	24 pleural mesotheliomas Incidence rate ratio for living <500 m to asbestos plant: 56.5 (Ref residence >2000-10000m of the asbestos plant) highest incidence rate ratio for pleural mesothelioma (161.9) found in the southeast quadrant of the 500-m area, coinciding with the predominant wind direction

Author	Country	Exposure type	Design	Period	Study population	Data Sources	Exposure assessment	Results
Wei et al 2012 [74]	China	Environmental exposure (Naturally occurring asbestos)	Cohort	2007-2010	Confirmed deceased cases in Dayao from 2007 to 2010	Center for Disease Control database Prevention of Dayao County database	SIG	higher mortality rates of mesothelioma and other cancer in Area I implying that environmental exposure to asbestos derived from outcropped asbestos in soil and rocks in the area may elevate mortality rates of cancers

Table S4:Summary of recent reviewed studies related to the relationship between other elongated mineral particles exposure and pleural mesothelioma (2010-2017).

Authors	Country	Exposure	Study Period	Study design	Study population	Mesothelioma cases	Data collection	Exposure assessment	Results
Erionite									
Metintas et al. 2010 [75]	Turkey	Erionite	1990-2006	cross-sectional	Population of Karain Village (n=322) (ref world population)	Death certificates (n=52)	Clinical and medical records Death certificates Interviews of residents	Samples from houses and analyses	SMR Men: 687.5 (95%CI 447.6-1032.5) Women: 1666.7 (95%CI 1134.1-2319.7)
Ortega-Guerrero et al. 2014 [76]	Mexico	Erionite	2000-2012	cross-sectional	Population of Tierra Blanca (n=254) (ref population of Guanajuato)	Histologically confirmed cases in Terra Blanca (n=4)	Clinical and medical records Mortality database Interview of family members	Mineralogical and chemical characterization of 206 samples of rocks, soils and building materials	Age-specific mortality rate / 1000 persons/year Men : 2.48 (95% CI 0.49 to 8.90) Women: 1.05 (95% CI 0.03 to 6.26)
Vermiculite									
Dunning et al. 2012 [77]	United States	Vermiculite	1980-2011	Cohort	Workers (white men) from an Ohio manufacturing facility (n=465) (ref US population)	Death certificates (n=2; 1.5%)	Questionnaire : work history, asbestos exposure	Historical measurement	SMR = 10.5 (95% CI 1.3-38.0)
Larson et al. 2010 [78]	United States	Vermiculite	1960-2006	Cohort	1862 vermiculite workers cohort (ref US population)	Death certificates (n=19)	Company records	Historical measurement Expertise	SMR = 94.8 (95%CI 57.0-148.0) Dose-response relationship with cumulative exposure

Authors	Country	Exposure	Study Period	Study design	Study population	Mesothelioma cases	Data collection	Exposure assessment	Results
Moolgavkaret al. 2010 [79]	United States	Vermiculite	1982-2001	Cohort	1,662 white male subjects enumerated in 1982 who had worked as vermiculite miners, millers, and processors at Libby, Montana (ref US population)	Death certificates (n=6)	Company records	Job exposure matrix	Km= 0.5 × 10−8, 95% CI = [0.3 × 10−8, 0.8 × 10−8].
Fluoro-edenite									
Bruno et al. 2014 [80]	Italy	Fluoro-edenite	1998-2011	Case cohort	Population of Biancavilla municipality (ref regional population)	cases classified as “certain” (histologically confirmed), “probable” or “possible” (n=45)	ReNaM registry Medical records Interview of cases or next-of-kins	Expertise	SIR Total : 5.76 (95% CI 3.76-8.44) Men : 3.69 (95% CI 1.97-6.32) Women : 13.08 (95% CI 6.97-22.00)
Conti et al. 2014 [81]	Italy	Fluoro-edenite	2003-2010	cross-sectional	Biancavilla residents (ref Sicilian population)	Death certificates (n=5) Hospitalization records (n=7)	Medical records Mortality database Demographic database		SMR Men : 379 (90% CI 149-797) Women : 1128 (90% CI 491-2226) Standardized hospitalization ratio Men: 261 (90% CI 122-489) Women : 780 (90% CI 366-1464)
Other EMPs									

Authors	Country	Exposure	Study Period	Study design	Study population	Mesothelioma cases	Data collection	Exposure assessment	Results
Abakay et al. 2016 [82]	Turkey	Ophiolites	2008-2013	cross-sectional	Population of Diyarbakir	Histologically confirmed cases (n=180)	Medical records Interview with subjects	SIG	Mean incidence /100 000 In Naturally occuring asbestos area (NOA) : 1059.5 <10 km from NOA area : 499.2 >10 km from NOA area : 240.1
Bayramet al. 2013 [83]	Turkey	Ophiolites	2000-2010	Case-Control	Population of Sivas	Cases identified from the cancer registry (n=100) Cancer controls (n=161)	Cancer registry Demographic database	SIG	OR for distance of birthplaces to ophiolites units Men: 1.68, IC95% CI 1.39-2.04 Women: 2.15 IC95% CI 1.69-2.74
Baumann et al. 2015 [84]	United States	Naturally occurring amphibole	1999-2010	Case cohort	Population of Nevada	Death certificates (n=31526)	Demographic database	Published data describing the presence of fibrous mineral in Nevada	MM sex-ratio M:F In southern Nevada counties of Clark and Nye: 2.69:1 In all Nevada counties, excluding the southern Nevada counties of Clark and Nye: 6.33:1 In all other US counties : 4.97:1 Proportion of young cases In southern Nevada counties of Clark and Nye: 11.28% In all Nevada counties, excluding the southern Nevada counties of Clark and Nye: 9.09% In all other US counties : 6.21%

Authors	Country	Exposure	Study Period	Study design	Study population	Mesothelioma cases	Data collection	Exposure assessment	Results
Allen et al 2014 [85]	USA	Taconite	1960-2010	Cohort	Minnesota taconite mining workers employed in 1983 for at least 1 year (n=68737) (ref Minnesota population)	Death certificates (n=30)	Company records	Duration of employment 1 year/ 2–5 years/ 6–14 year/ 15+ years	SMR=2.77 (95% CI 1.87- 3.96)
Lambert, C. et al 2016 [86]	USA	Taconite		Nested case–control	Minnesota taconite mining workers employed in 1983 for at least 1 year (n=68737)	Deceased cases (n=80 men) 4 controls matched controls by age (n=315)	Company records	Historical measurement Job exposure matrix	Duration of employment RR=1.03 (95%CI 1.00-1.06) Cumulative EMP RR=1.10 (95%CI 0.97-1.24)
Finkelstein et al. 2012 [87]	United States	Talc ore	1990-2007	cohort	New York Talc mining and milling workers who worked at least 1 day from 1948-1989 (n=782)	Death certificates	Company records Personal interview		Incidence rates at leats 5 (1.6-11.7) times the rate in the general population
Synthetic fibers									

Authors	Country	Exposure	Study Period	Study design	Study population	Mesothelioma cases	Data collection	Exposure assessment	Results
Walker et al. 2012 [88]	United States	Refractory ceramic fibers	1970-2008	Cohort	Workers employed in RCF factories since 1950 (n=605) 605 cohort members engaged in the manufacture of RCF and followed since 1987 to cancer rates	Death certificates	Company records Personal interview	Historical measurement Job exposure matrix	No deaths from mesothelioma as compared to 4.9 anticipated under a crocidolite-like hypothesis (p = 0.007), 1.0 for amosite (p = 0.38) and 0.05 for chrysotile (p = 0.95)
Lemastrers et al. 2017 [89]	United States	Refractory ceramic fibers	1987-2014	Cohort	Workers employed at five RCF facilities from 1987-1999 (n=1119)	Death certificates	Company records Personal interview	Historical measurement Job exposure matrix	1 mesothelioma death SMR=2.86 (95% CI: 0.07-15.93)

Table S5: Biomarkers and pleural mesothelioma in retrospective studies: diagnostic value. Selection of initial studies, recent studies and meta-analysis.

Study (country)	Population (type, number of subjects)	Biomarker (in serum or plasma)	cut off value	Se	Sp	Comments
Mesothelin and related peptides (including megakaryocyte potentiating factor)						
Robinson et al 2003 [130] (Australia)	• 44 MM (39 men, 5 woman) • 68 healthy controls (40 asbestos-exposed and 28 non asbestos-exposed) • 38 non mesothelioma pleural diseases (16 pleural plaques) • 30 malignant non-pleural diseases • 92 inflammatory non-pleural lung disease	Mesothelin (serum) (specific ELISA with OV569 and 4H3 monoclonal antibodies)	Absorbance ≥ 0.218 (mean value of non asbestos-exposed healthy subjects +3SD)	84% (a)	95% (a)	- 3 of the 7 positive asbestos-exposed control developed mesothelioma within 1-5 years - None of the 33 negative asbestos controls developed mesothelioma during an 8 years follow-up - Se and Sp were calculated here comparing MM cases (n=44) to a group including all other subjects except non asbestos healthy subjects (n=200). Sp value was 82.5% when controls were restricted to asbestos-exposed healthy subjects.
Hollevoet et al 2010 [131] (Belgium)	Six cohort of subjects • 85 MPM (median age = 65 years) • 101 healthy unexposed controls (median age = 56 years) • 89 healthy asbestos-exposed (median age = 52 years) • 123 benign asbestos-related disease (median age = 64 years) • 46 benign respiratory disease (median age = 62 years) • 63 lung cancer (median age = 65 years)	Megakaryocyte potentiating factor (MPF) ELISA Kit (serum) Soluble mesothelin (Mesomark Cis bio ELISA Kit) in serum	13.46 ng/mL 1.89 nmol /L	68% 66%	97% 94%	- MPF and soluble mesothelin have an equivalent diagnostic performance - MPF and soluble mesothelin levels highly correlated
Bayram et al 2014 * [132] (Turkey)	• 24 MPM (mean age = 57.8 ± 12.7 years) • 279 pleural plaques (mean age = 63.1 ± 11.5 years) • 123 healthy exposed (mean age = 63.3 ± 9.8 years) • 120 controls (mean age = 61.6 ± 10.8 years)	Mesothelin (serum) (Fujirebio ELISA Kit)	1.63 ng/L	58%	83%	- Se and Sp evaluated when mesothelioma subjects were compared to the 3 other groups

Creaney et al 2014 [133] (Australia)	• 82 MPM (mean age = 70 years) • 49 benign asbestos related pulmonary diseases (mean age = 77 years) • 35 non-malignant effusions (mean age = 68 years) • 36 malignant effusions (mean age = 67 years)	Mesothelin (plasma) (Mesomark Fujirebio ELISA Kit) Fibulin 3 (plasma) (USCN Life Science Inc ELISA Kit)	2.5 nM/mL 53 ng/mL	56% 22%	96% 95%	- MPM compared to the 3 others groups - Mesothelin remains the clinically useful mesothelioma biomarker - MPM compared to the 3 others groups
Luo et al 2010 [134] (several countries)	*Meta-analysis (11 studies until march 2008)* • *717 MM* • *2,851 controls (with various histories of asbestos exposure and/or asbestos-related disease*	*SMRP (ELISA) (8 studies on soluble mesothelin, 3 on megakaryocyte potentially factor)*	*Various values among the studies included in the meta-analysis*	*64% [95%CI = 61%-68%]*	*89% [95%CI = 88%-90%)*	- *Significant heterogeneity between studies (Se ranging from 41% to 91%, Sp from 73% to 100%).*
Hollevoet et al 2012 [135] Several countries)	*Meta-analysis on 4,491 patients (median age = 62 years)* • *1,026 MPM (median age = 66 years)* • *778 lung cancer (median age = 65 years)* • *267 benign respiratory disease (median age = 65 years)* • *736 benign asbestos-related disease (median age = 63 years)* • *775 healthy asbestos-exposed (median age = 54 years)* • *909 healthy (median age = 56 years)*	*Mesothelin (serum) (MesomarkFujirebio ELISA Kit)*	*2nmol/L*	*47%*	*96%*	*When applying a common threshold of 2nmol/L; sensitivities varied from 19% to 68% according to the studies, and specificities from 88% to 100%* *At a selected specificity of 95%, sensitivity was 32% (95% CI = 26% to 40%) when analysis was restricted to 217 subjects with early diagnosis of MM (stage I or II, epithelioid or biphasic type) and 1,612 symptomatic or high risk controls.*
Osteopontin						
Pass et al 2005 [136] (USA)	• 76 MPM (mean age = 65 ±1 year) • 69 asbestos-related non malignant pulmonary disease (mean age = 65±1 year) • 45 subjects without exposure	Osteopontin (ELISA Assay)	48.3 ng/mL	77.6%	85.5%	Se and Sp were calculated comparing MM cases and the group exposed to asbestos

Bayram et al 2014 * [132] (Turkey)	• 24 MPM (mean age = 57.8 ± 12.7 years) • 279 pleural plaques (mean age = 63.1 ± 11.5 years) • 123 healthy exposed (mean age = 63.3 ± 9.8 years) • 120 controls (mean age = 61.6 ± 10.8 years)	Osteopontin (serum) (Ray bio ELISA Kit)	17.273 ng/L	75%	86%	- Se and Sp evaluated when mesothelioma subjects were compared to the 3 other groups
Hu et al 2014 [137] (several countries)	*Meta-analysis (6 studies until march 2013)* • *356 MPM* • *546 controls (with various histories of asbestos exposure and/or asbestos related diseases. Some were healthy controls without asbestos exposure).*	*Osteopontin (In serum and / or plasma)*	*Various values among the studies included in the meta-analysis.*	*65% [95%CI = 60%-70%]*	*81% [95%CI = 78%-85%]*	- *Diagnostic accuracy of serum and plasma osteopontin was comparable* - *Great heterogeneity among the included studies (Se ranging from 41% to 96%, Sp from 26% to 96%)*
Fibulin3						
Pass et al 2012 [138] (USA and Canada)	Three cohorts originating from Detroit, New-York and Toronto. Total of patients : • 92 MM patients (USA) • 136 asbestos-exposed subjects without cancer • 93 patients with effusions (not mesothelioma) • 43 healthy controls	Fibulin-3 (plasma) (ELISA USCN life Science)	52.8 ng/mL	96.7%	95.5%	- No variation of plasma fibulin-3 level according to age, sex, duration of asbestos exposure or radiographic changes - Se and Sp calculated when MM patients (n = 92) were compared to other cohorts (n = 290) - Validation cohorts were used: serum samples (no plasma available) from 49 asbestos-exposed subjects in whom mesothelioma developed and 96 asbestos-exposed cancer-free controls from Carotene and Retinol Efficacy Trial (CARET), and also 48 plasma samples of mesothelioma patients and 96 asbestos-exposed cancer-free persons from Toronto Princess Margaret Hospital. No discrimination between MPM patients and controls in the CARET serum old archived samples. In the Canadian population, at a cut-off value of 28.96ng/mL, Se was 72.9% and Sp 88.56%

Pei et al 2017 [139] *(several countries)*	*Meta-analysis (7 studies)* • *468 MPM* • *664 controls (cancer-free individuals, but with various asbestos exposure and/or diseases)*	*Fibulin-3 (all samples)* *(serum)* *(plasma)*	*Various values according to studies and type of biological sample*	*62% [95%CI = 45%-77%]* *77% [95%CI = 71%-83%)* *54% [95%CI = 50%-58%]*	*82% [95%CI = 73%-89%]* *85% [95%CI = 79%-90%]* *77% [95%CI = 74%-80%]*	- *Heterogeneity between the studies.* - *Role of the test matrix : studies with serum-based analysis harbored better accuracy that these with plasma-based analysis*
Micro RNA						
Kirschner at al 2012 [140] (Australia)	Test cohort • 15 MM • 14 healthy controls Validation cohort • 30 MM • 10 asbestosis	854 mi RNA				- miR-625-3p significantly elevated in the serum of MM patients compared with asbestosis controls in the validation cohort
Santarelli et al 2015 [141] (Italy)	• 45 MPM patients (mean age = 69 ± 8 years) • 99 asbestos exposed subjects (mean age : 64 ± 10 years) • 44 healthy controls (mean age = 68 ± 6 years)	miRNA-126 methylated thrombomodulin promoter (Met-TM)		75% -	54% 82%	Combination of miR-126 with Met-TM and SMRP allowed better differentiation of the subjects having MM and control group. The biomarkers were independent of age, gender, smoking and duration of exposure. A validation cohort was used = 18 patients with MM, 50 asbestos exposed subjects, 20 controls and 42 lung cancer cases.
Bononi et al 2016 [142] (Italy)	• 10 MPM • 10 healthy exposed • 10 controls	Micro RNA (1,201 miRNAassessed)		-	-	miR-197-3p, miR-1281 and miR-32-3p are up-regulated in MPM subjects
Weber et al 2017 [143] (Germany)	Discovery phase • 21 male patients with MPM (median age = 72 years) • 21 cancer-free male exposed to asbestos Verification phase • 22 MPM • 44 controls exposed to asbestos	miRNA (plasma) Specific study of miR-16, miR-24, miR-28-3p, miR-126 miR-132-3p, miR-146b-5p, miR-625-3p, U6 snRNA miR-132-3p miR-132-3p and miR126		 86% 77%	 61% 86%	MPM and controls were matched for age and smoking status. MiR-132-3p shows different expression levels in plasma between MPM subjects and cancer-free controls formerly exposed to asbestos

HMGB1						
Napolitano et al 2016 [144] (USA and UK)	• 22 MM patients (mean age = 66 years) • 20 asbestos exposed insulators subjects • 13 benign pleural effusions • 25 malignant pleural effusions • 20 healthy controls from UK	Total HMGB1 (serum and plasma) Hyper acetylated HMGB1	15.75 ng/mL 2 ng/mL	72.3% 100%	100% 100%	- Se and Sp calculated for comparison of MM with asbestos exposed subjects healthy controls - Total HMGB1 and hyper-acetylate HMGB1 also differentiated MM patients from individuals with pleural effusions due to other causes (but with different cut-off values) - Total and hyper-acetylated HMGB1 did not correlated with any of the other biomarkers tested (mesothelin, osteopontin, fibulin-3) among MM patients - Combining HMGB1 and fibulin-3 provided increased sensitivity and specificity in differentiating MM patients from patients with benign or malignant non MM pleural effusion
Ying et al 2017 [145] (China)	497 subjects • 15 MPM (median age = 66 years) • 71 healthy without any asbestos exposure (median age = 67 years) • 170 exposed to asbestos < 10 years with normal chest X-ray (median age = 66 years) • 129 exposed to asbestos > 10 years with normal chest X-ray (median age = 67 years) • 81 pleural plaques (median age = 68 years) • 31 asbestosis (median age = 73 years)	HMGB1 (Cloud Clone Corp ELISA Kit) (serum)	52.29 ng/mL 52.39 ng/mL	100% 100%	57.6% 57.4%	- Se and Sp on the two lines are reported for cut-off values when comparing MPM subjects with asbestos-exposed subjects during less than 10 years and more than 10 years, respectively. - Even if mean HMGB1 levels were significantly higher in asbestosis and MPM groups than in other groups, there was a large overlap of individual values of serum HMGB1 levels, in the six groups of subjects
Other tests						
Onda et al 2006 [146] (USA)	• 56 MM (all of epithelial type) (median age = 57 years) • 70 healthy controls (median age = 39 years)	Megakaryocite potentiation factor (MPF) (serum) Construction of a new specific ELISA test	Absorbance ≥ 0.034	91%	100%	- Initial methodological study : - 56 cases with MM had advanced disease.
Ostroff et al 2012 [147] (USA)	Case-control design • 117 MM (median age = 64 years) • 142 asbestos-exposed controls (including subjects with asbestosis, pleural plaques)	SOMAscan proteomic assay = Slow Off-rate Modified Aptamers quantification of proteins in biological samples (1045 proteins)				- 60 cases and 60 controls for training, 19 cases and 20 controls for validation, 38 cases and 62 controls for validation - Identification of 64 candidate biomarkers. 13 biomarkers retained in the validation assay

Watzka et al 2013 [148] (USA)	• 101 MPM (73 epithelioid type) • 96 asbestos-exposed healthy insulation male workers	Integrin linked Kinase (ILK) (serum) ELISA assay	4.49 ng/mL	61.4%	80.2%	No influence of the histological type of MPM on the level of ILK serum concentration
Xu et al 2015 [149] (Japan)	• 10 mesothelioma (mean age = 69.9 ± 5.6 years) • 172 healthy subjects possibly exposed to asbestos (mean age = 65.7 ± 8.8 years) • 76 healthy subjects unexposed to asbestos (mean age = 50.9 ± 7.7 years) • 532 subjects possibly exposed to asbestos • 412 pleural plaques • 10 benign hydrothorax • 86 asbestosis • 17 lung cancer	CCL3 (Chemokine ligand 3) (serum) (Quantikine Human CCL3 / MIP-1a Immunoassay Kit, (R&D Systems)	7.8 pg/mL (limit of detection)	-	-	- No significant difference in the level of CCL3 in the unexposed group and the healthy asymptomatic subjects possibly exposed to asbestos where CCL3 was detectable in 6.6% and 30.2% respectively. - Very high level of CCL3 in 3 subjects with mesothelioma (CCL3 detectable in 9 out of 10 subjects with mesothelioma).
Demir et al 2016 [150] (Turkey)	• 42 MPM (mean age = 60.7 ± 11.4 years) • 48 asbestos exposed subjects (mean age = 59.1 ± 13.3 years (27 with pleural plaques)	Thioredoxu1 (TRX, serum) Epidermal growth factor receptor (EGFR, serum)	156,67 ng/mL 19.96 ng/mL	92.9% 90.5%	77.6% 64.4%	- The MPM group had significantly higher levels of EGFR, TRX, SMRP and fibulin-3 levels than other groups
Morré et al 2016 [151] (Autralia)	• 17 MPM (mean age = 67 years) • 15 asbestos exposed (pleural plaques or asbestosis) (mean age = 72 years)	Ecto-nicotinamide ademine nucleotide oxidase disulfide-thiol exchanger 2 (ENOX2) transcripts				- ENCX2 protein transcript variants were present in serum 4 to 10 years before clinical symptoms of mesothelioma
Johnen et al 2017 [152] (Australia and Germany)	• 163 + 36 MPM • 163 + 72 controls (asbestosis or pleural plaques)	Calretinin (plasma and serum)	0.85 ng/mL	71%	95%	- Calretinin is specific for epithelioid and biphasic MPM - Performance was roughly similar to mesothelin (Se 69%, Sp 95%) in this series for non-sarcomatoid MPM

n : number

MPM : malignant pleural mesothelioma ; MM : malignant mesothelioma ; Se : sensibility ; SMRP : soluble mesothelin related peptide ; Sp : specificity ;

Table S6: Biomarkers and screening of mesothelioma: Follow-up studies of asbestos exposed cohorts

Study (country)	Population (type, number of subjects, age, period/duration of follow-up)	Biomarker (in serum or plasma	Threshold cut off value	Positive samples	Se	Sp	NPV	PPV	Comments
Park et al 2008 [158] (Australia)	n = 538 subjects (mean age = 66.9 years) • 20 silicosis • 24 asbestosis • 113 DPT • 142 pleural plaques • 13 asbestosis + DPT Follow-up = 1 year	Mesothelin (serum) (MesomarkFujirebio ELISA assay)	2.5 nM/L	n = 15	Not evaluable (a)	97.2% (a)	100% (a)	0% (a) (0/15)	No mesothelioma case 15 false positive cases i.e (100% positive cases)
Hollevoet et al 2011 [159] (Belgium)	n = 215 asbestos exposed workers (mean age = 55.7 years) • 71 pleural plaques • 39 DPT • 16 others (asbestosis++) • 89 healthyasbestosexposed Follow-up = 2 years	Mesothelin (serum) (Mesomark Cis bio ELISA assay) MPF (Medical and Biological Laboratories Nagano ELISA Assay)	2.10 nM/L 13.1 ng/mL	n = 20 n = 21	0% (a) 0%	91% (a) 90.6%	99.5% (a) 99.5% (a)	0% (a) (0/20) 0% (0/21) (a)	- Longitudinal biomarker analysis performed in a subgroup, showing that biomarker levels increased during follow-up (role of age and glomerular filtration rate) - 14 subjects having both mesothelin and MPF markers elevated at baseline - 1 mesothelioma during follow-up (subject with pleural plaques) - 100% false positives for both markers
Gube et al 2011 [160] (Germany)	n = 626 asbestos exposed workers (mean age = 63 years) Mean follow-up (mortality study) : 10 to 14 years all previously exposed to asbestos	Mesothelin (serum) (Mesomark Fujirebio ELISA Kit) CYFRA21-1 (Elecsys 2010 System, Roche) CA125 (ADVIA Centaur System, Bayer)	1.5 nM/L 3.3 ng/mL 34 KIU/L	n = 52 n = 10 n = 26	10% (a) 0% (a) 5% (a)	91.8% (a) 98.4% (a) 95.9% (a)	96.9% (a) 96.8% (a) 96.9% (a)	3.9% (a) 0% (a) 3.9% (a)	- Subjects recruited between 1993 and 1997, mortality follow-up until April 30 2007. Mean duration of asbestos exposure = 25 years (minimum = 3, maximum = 45) - Archived serum samples collected between 1993 and 1997 - 20 mesothelioma cases and 12 lung cancer cases - Combination of biomarkers increased sensibility up to 15% (mesothelin + CA125) but with low PPV and high number of false positive cases (n = 71)

Felten et al 2014 [161] (Germany)	n = 2,262 (mean age : 59 years) • 1894 asbestos exposed power industry workers • 266 subjects with unknown history of asbestos exposure • 102 controls (unexposed to asbestos) Follow-up = 7 months to 4 years	Mesothelin (serum) (Mesomark CIS Bio ELISA Kit) Osteopontin (IBL ELISA Kit, Hamburg)	1.4 nM/L 900 ng/mL	n = 134 in exposed workers n = 43 in exposed workers	20% (a) 0% (a)	93.2% (a) 98% (a)	99.7% (a) 99.7% (a)	0.7% (a) 0% (a)	- Blood samples collected between October 2005 and May 2009 - Several samples obtained in some participants. - Follow-up until the end 2009 - Influence of age on markers level. No effect of duration of asbestos exposure or presence of benign pleural disease - Fixed cut-off values for evaluated biomarkers appeared inadequate - 5 mesothelioma cases in power industry workers (and 11 cases of lung cancer) - High number of false positive cases (133 for mesothelin, 43 for osteopontin - Some indication of increase of mesothelin level 6 to 18 months before clinical symptoms of mesothelioma
Filiberti et al 2014 [162] (Italy)	N = 1,714 asbestos exposed subjects (dock/shipyard, iron and steel-mill industries) (mean age = 62.2 years) Median follow-up 47.1 months (range 5 – 58.6 months) • 1,227 healthy subjects • 152 asbestos-related pleural lesions • 24 asbestosis • 182 other benign diseases • 118 cancers	Mesothelin (serum) (Mesomark Fujirebio ELISA Kit)	1.5 nM/L	40	0% (a)	97.8% (a)	99.8% (a)	0% (a) 0/40	- Duration of asbestos exposure ≥ 1 year - Blood sampling at 1 and 2 years of follow-up in 1,629 subjects - 3 mesothelioma cases during follow-up + 1 case diagnosed at first visit - Correlation between age and mesothelin level, and inverse correlation between body mass index and mesothelin level

Hirohashi et al 2014 [163] (Japan)	5 years screening of Tokyo general construction workers n = 40,000	N-ERC / mesothelin (ELISA assay)	8 ng/mL		100% (2/2) (a)	100% (a)	100% (a)	0.2% (2/714) (a)	- As of September 26,2010, 40,000 participants and 124,288 blood samples collected and analyzed 1,603 with abnormal values. 714 samples confirmed after reanalysis. Finally, 62 participants identified as “high risk population” by the case review committee : i.e : i) level NERC/mesothelin> 8ng/mL and ii) age ≥ 35 years, iii) absence of renal dysfunction, iv) human anti-mouse antibody not detected. - Low risk population N-ERC / mesothelin measurements with no abnormal values at least twice. n = 7850 subjects - 2 cases of mesothelioma in the high risk group - PPV was 3.2% when analysis was restricted to participants identified as “high risk population” according to the criteria of the case review committee.

n : number ;

(a) Calculated from data of the original manuscript

DPT : Diffuse pleural thickening ; MPF : megakaryocyte potentiating factor ; NPV : Negative predictive value ; PPV : positive predictive value ; Se : sensibility ; SMRP : soluble mesothelin related peptide ; Sp : specificity

Table S7: Biomarkers and early detection of mesothelioma in other retrospective case-control studies based on archived samples with longitudinal survey

Study (country)	Population (type, number of subjects, age, period/duration of follow-up)	Biomarker (in serum or plasma	Threshold cut off value	Positive samples	Se	Sp	NPV	PPV	Comments
Creaney et al 2010 [164] (Australia)	Retrospective longitudinal evaluation • 106 mesothelioma (87 MPM) with serum samples available before diagnosis (mean age = 66 years) Median timing of sample = 8 months before diagnosis • 99 asbestos exposed subjects (0.1 to 253 f-years/ml) • 109 non asbestos exposed healthy subjects (controls have follow-up of 10 years malignancy free period)	Mesothelin (serum) (Mesomark, Fujirebio ELISA Kit)	2.5 nM	17 1 (a) 3 (a)	16% (a)	98.1% (a)	71%	80.9% (17/21)	- No correlation between mesothelin concentration and degree of asbestos exposure in asbestos-exposed subjects - 17 subjects of the 106 mesothelioma cases had elevated mesothelin levels before pathologic diagnosis. No link with sex, age, histology, site of tumor, radiological changes in these mesothelioma subjects. - Elevated mesothelin in one asbestos exposed subject was related to renal dysfunction.

n : number ;

(a) Calculated from data of the original manuscript

DPT : Diffuse pleural thickening ; MPF : megakaryocyte potentiating factor ; NPV : Negative predictive value ; PPV : positive predictive value ; Se : sensibility ; SMRP : soluble mesothelin related peptide ; Sp : specificity

Table S8: Simulations of the expected number (%) of false positive tests and false negative tests from real-life use of biological markers according to a specificity of 95%, different scenario of sensitivity (32%, 50%, 60%, 70%) and several lifetime risks of mesothelioma (15%, 10%, 5%, 2.5%, 2%, 1.5%, 1%, 0.5%).

	Se=0.32 / Sp=0.95			Se=0.50 / Sp=0.95			Se=0.60 / Sp=0.95			Se=0.70 / Sp=0.95		
	Mesothelioma			Mesothelioma			Mesothelioma			Mesothelioma		
	Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total
Lifetime risk of mesothelioma: 15%												
Test +	480	425	905	750	425	1,175	900	425	1,325	1,050	425	1,475
Test-	1,020	8,075	9,095	750	8,075	8,825	600	8,075	8,675	450	8,075	8,525
Total	1,500	8,500	10,000	1,500	8,500	10,000	1,500	8,500	10,000	1,500	8,500	10,000
False positive (%)		**47.0**			**36.2**			**32.1**			**28.8**	
False negative (%)		**11.2**			**8.5**			**6.9**			**5.3**	
Lifetime risk of mesothelioma: 10%												
Test +	320	450	770	500	450	950	600	450	1,050	700	450	1,150
Test-	680	8,550	9,230	500	8,550	9,050	400	8,550	8,950	300	8,550	8,850
Total	1,000	9,000	10,000	1,000	9,000	10,000	1,000	9,000	10,000	1,000	9,000	10,000
False positive (%)		**58.4**			**47.4**			**42.9**			**39.1**	
False negative (%)		**7.4**			**5.5**			**4.5**			**3.4**	
Lifetime risk of mesothelioma: 5%												
Test +	160	475	635	250	475	725	300	475	775	350	475	825
Test-	340	9,025	9,365	250	9,025	9,275	200	9,025	9,225	150	9,025	9,175
Total	500	9,500	10,000	500	9,500	10,000	500	9,500	10,000	500	9,500	10,000
False positive (%)		**74.8**			**65.5**			**61.3**			**57.6**	
False negative (%)		**3.6**			**2.7**			**2.2**			**1.6**	
Lifetime risk of mesothelioma: 2.5%												
Test +	80	488	568	125	488	613	150	488	638	175	488	663
Test-	170	9,263	9,433	125	9,263	9,388	100	9,263	9,363	75	9,263	9,338
Total	250	9,750	10,000	250	9,750	10,000	250	9,750	10,000	250	9,750	10,000
False positive (%)		**85.9**			**79.6**			**76.5**			**73.6**	
False negative (%)		**1.8**			**1.3**			**4.1**			**0.8**	

Table S8 (continue): Simulations of the expected number (%) of false positive tests and false negative tests from real-life use of biological markers according to a specificity of 95%, different scenario of sensitivity (32%, 50%, 60%, 70%) and several lifetime risks of mesothelioma (15%, 10%, 5%, 2.5%, 2%, 1.5%, 1%, 0.5%).

	Se=0.32 / Sp=0.95			Se=0.50 / Sp=0.95			Se=0.60 / Sp=0.95			Se=0.70 / Sp=0.95		
	Mesothelioma			Mesothelioma			Mesothelioma			Mesothelioma		
	Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total
Lifetime risk of mesothelioma: 2%												
Test +	64	490	554	100	490	590	120	490	610	140	490	630
Test-	136	9,310	9,446	100	9,310	9,410	80	9,310	9,390	60	9,310	9,370
Total	200	9,800	10,000	200	9,800	10,000	200	9,800	10,000	200	9,800	10,000
False positive (%)		**88.4**			**83.0**			**80.3**			**77.8**	
False negative (%)		**1.4**			**1.1**			**0.8**			**0.6**	
Lifetime risk of mesothelioma: 1.5%												
Test +	48	493	541	75	493	568	90	493	583	105	493	598
Test-	102	9,358	9,460	75	9,358	9,433	60	9,358	9,418	45	9,358	9,403
Total	150	9,850	10,000	150	9,850	10,000	150	9,850	10,000	150	9,850	10,000
False positive (%)		**91.1**			**86.8**			**84.5**			**82.4**	
False negative (%)		**1.1**			**0.8**			**0.6**			**0.5**	
Lifetime risk of mesothelioma: 1%												
Test +	32	495	527	50	495	545	60	495	555	70	495	565
Test-	68	9,405	9,473	50	9,405	9,455	40	9,405	9,445	30	9,405	9,435
Total	100	9,900	10,000	100	9,900	10,000	100	9,900	10,000	100	9,900	10,000
False positive (%)		**93.9**			**90.8**			**89.2**			**87.6**	
False negative (%)		**0.7**			**0.5**			**0.4**			**0.3**	
Lifetime risk of mesothelioma: 0.5%												
Test +	16	498	514	25	498	523	30	498	528	35	498	533
Test-	34	9,453	9,487	25	9,453	9,478	20	9,453	9,473	15	9,453	9,468
Total	50	9,950	10,000	50	9,950	10,000	50	9,950	10,000	50	9,950	10,000
False positive (%)		**96.9**			**95.2**			**94.3**			**93.4**	
False negative (%)		**0.4**			**0.3**			**0.2**			**0.2**	

Table S9. Immunohistochemical analysis in epithelioid mesothelioma

Mesothelial Markers	**sensitivity**	**Specificity versus lung adenocarcinoma**
Calretinin (poly)	>90%	90-95%
WT1 (cl 6FH2)	70-75%	~100%
CK5/6	75%–100%	80%–90%
D240 (Cl.D2-40))		
EMAm (cl E29)	77%	77%
Mesothelin (cl.A103)	88%	73%
Adenocarcinoma markers (positive epithelial markers)		
B72.3 (cl)	25-85%	95%
BerEP4(Cl)	95-100%	74-87%
BG8 (cl)	90-100%	93-97%
ACE moabs	80-100%	>95%
Organ specific markers Lung		
TTF-1 (cl.8G7G3/1)	~80%	High
Napsin A	~80%	High
Organ specific –Breast carcinoma metastasis		
Estrogen receptor α(cl.EP1))	NA	NA
Progesterone receptor	NA	NA
GCDFP15	30-40%	High
Mammaglobin	50-85%	High
Organ specific –Renal carcinoma metastasis		
PAX8 (Poly)	70-100%	Unknown
PAX2	80%	Unknown
RCC (cl.PN-15)	<85%	75-95%
CD15	60%	High
BAP-1	~50-70%	NA

Adapted from Travis 2015 [297] and Righi 2016 [298] ; variable by subtype; NA=Not available

Table S10. Immunohistochemical analysis in sarcomatoid mesothelioma	
Mesothelial markers	**% of positivity in Sarcomatoid mesothelioma**
Keratin AE1/AE3	~90%
CAM5.2	~90%
CK5/6	~30%
Calretinin (nuclear staining)	~50% often focal
WT1	~45%
D240	>70%
GATA3	85% sensitivity and 100% specificity
BAP1	22%

Adapted from Travis 2015 [297], Righi 2016 [298] et Marchevsky 2017 [299].

Table S11. Immunohistochemical analysis in sarcomatoid carcinoma metastatic to the pleura	
Mesothelial markers	**% of positivity in sarcomatoid carcinoma**
Keratin AE1/AE3	~88%
CAM 5.2	~91%
Calretinin	<40%
TTF-1 (cl. 8G7G3/1)	~17%
P40 (cl.BC28)	0
BAP1 (cl.C-4)	<1%

Table S12. Characteristics of studies assessing first-line treatments in malignant pleural mesothelioma.

Reference	Design	N pts	Treatment	Results based on primary endpoint	Conclusion
Targeted therapies					
Laurie, 2011 [249]	Phase II	18	Sunitinib	1 response among 18 pts.	Negative
Buikhuisen, 2013 [250]	Phase III	222	Maintenance thalidomide	PFS: median 3.6 months (thalidomide) versus 3.5 months (HR=0.95; 95%CI: 0.73-1.20; p=0.72)	Negative
Buikhuisen, 2016 [251]	Phase II R	25	CDDP-PEM +/- Axitinib	11/11 and 16/20 had second thoracoscopy (No difference for RR, PFS, survival)	Negative (for common clinical criteria)
Dubey, 2010 [252]	Phase II	20	Sorafenib	RR 10%	Negative
Fennell, 2012 [253]	Phase II	10	Bortezomib	RR 0%	Negative
Hassan, 2014 [254]	Phase II	99	CDDP-PEM + Amatuximab	PFS rate at 6 months 51.3%	Negative
Jahan, 2012 [255]	Phase II	47	Vatalanib	PFS rate at 3 months 55%	Negative
Krug, 2014 [256]	Phase II R	65	CDDP-PEM +/- CBP501	PFS rate at 4 months 25/40 (63%) versus 9/23 (39%)	Positive
O'Brien, 2013 [257]	Phase II	82	CDDP-Bortezomib	PFS rate at 18 weeks 53%	Negative
Conventional chemotherapy					
Ralli, 2009 [258]	Phase II	25	GEM-DOC	No clear primary endpoint RR 28%, median overall survival 15 months (range: 12.4-17.5 months)	Positive (?)
Arrieta, 2012 [259]	Phase II	38	CDDP-liposomal DOX	No clear primary endpoint RR 38.9%, median PFS 4.6 months, median survival 19.6 months	Positive (?)
Habib, 2013 [260]	Phase II R	36	CDDP-GEM vs CBDCA-PEM	No clear primary endpoint RR 10% vs 15% (p=0.041)	?
Katirtzoglou, 2010 [261]	Phase II	62	CBDCA-PEM	RR 29%	Positive
Kovac, 2012 [262]	Phase II	78	CDDP-GEM	Survival: median 17 months	Positive
Kuribayashi, 2013 [263]	Phase II	21	MTX-GEM	No clear primary endpoint (RR 38.1%, median survival 19.4 months)	Positive (?)
Bevacizumab-based combination					
Zalcman, 2016 [264]	Phase III	458	CDDP-PEM +/- Bev	Survival: median 18.8 months vs 16.1 months (p = 0.0167)	Positive
Ceresoli, 2013 [265]	Phase II	76	CBDCA-PEM-	PFS: median 6.9 months	Negative

			Bev		
Dowell, 2012 [266]	Phase II	53	CDDP-PEM-Bev	PFS rate at 6 months 56%	Negative
Kindler, 2012 [267]	Phase II R	115	CDP-GEM +/- Bev	PFS: median 6.9 months vs 6 months (p = 0.88)	Negative

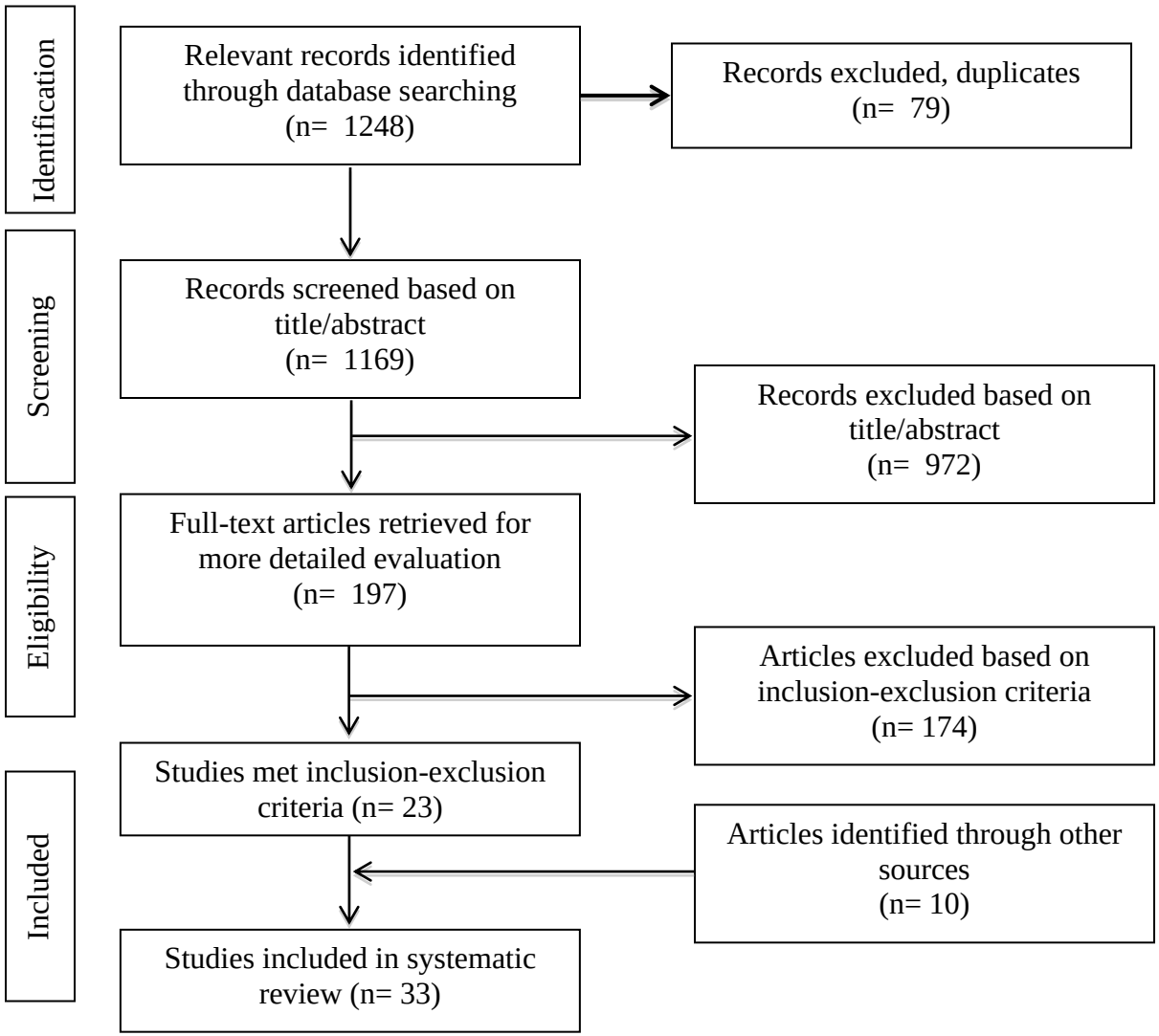
Pts : patients ; RR : response rate ; PFS : progression-free survival ; R : randomised ; CDDP : cisplatin ; PEM : pemetrexed ; GEM : gemcitabine ; DOC : docetaxel ; DOX : doxorubicin ; CBDCA : carboplatin ; MTX : methotrexate ; Bev : bevacizumab

Table S13. Studies assessing salvage therapy in malignant mesothelioma

Reference	Design	N pts	Treatment	Results based on primary endpoint	Conclusion
Targeted therapies					
Laurie, 2011 [249]	Phase II	17	Sunitinib	RR 0%	Negative
Dubey, 2010 [252]	Phase II	30	Sorafenib	RR 3.3%	Negative
Nowak, 2013 [268]	Phase II	30	BNC105P	RR 3%	Negative
Ou, 2015 [269]	Phase II	59	Everolimus	PFS rate at 4 months 29%	Negative
Papa, 2013 [270]	Phase II	53	Sorafenib	PFS rate at 6 months 36%	Positive
Wheatly-Price, 2016 [271]	Phase II	17	PF-03446962	RR 0%	Negative
Fennell, 2012 [253]	Phase II	23	Bortezomib	RR 4.8%	Negative
Campbell, 2012 [272]	Phase II	51	Cediranib	RR 10%	Negative
Dudek, 2012 [273]	Phase II	46	Dasatinib	PFS rate at 6 months 23%	Negative
Garland, 2011 [274]	Phase II	54	Cediranib	RR 9%	Negative
Ramalingam, 2009 [275]	Phase II	13	Belinostat	RR 0%	Negative
Scherpereel, 2011 [276]	Phase II	45	DOX-VPA	RR 16%	Positive
Krug, 2015 [277]	Phase III	661	Vorinostat versus placebo	Survival: median 30.7 weeks vs 27.1 weeks (p = 0.86)	Negative
Conventional chemotherapy					
Stebbing, 2009 [278]	Phase II	63	Vinorelbine	ORR 16%	Positive
Tourkantonis, 2011 [279]	Phase II	37	DOX-GEM	No clear primary endpoint (RR 38.1%, median survival19.4 months)	Positive (?)
Immunotherapy					
Calabro, 2013 [280]	Phase II	29	Tremelimumab	RR 7%	Negative
Calabro, 2015 [281]	Phase II	29	Tremelimumab	Immune related RR 13.8%	Negative
Maio, 2017 [282]	Phase III	571	Tremelimumab versus placebo	Survival: median 7.7 months vs 7.3 months (p = 0.41)	Negative
Gregorc, 2010 [283]	Phase II	57	NGR-hTNF	PFS rate at 12 weeks 38%	Negative

Pts : patients ; RR : response rate ; PFS : progression-free survival ; GEM : gemcitabine ; DOX : doxorubicin ; VPA : valproic acid

Figure S1. Flow chart of the search of the literature.



GRADE Evidence Profiles

Table S14: Should partial pleurectomy compared to talc pleurodesis be used as palliative surgery in patients with symptomatic malignant pleural mesothelioma?

Bibliography: 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: 1118-1127.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VATS partial pleurectomy	talc pleurodesis	Relative (95% CI)	Absolute (95% CI)		
Quality of life at 6 months (assessed with: EQ-5D (MID 0.074); Scale from: 0 (dead) to 1 (full health))												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	56	56	MD **0.08 higher** (0.003 higher to 0.16 higher)		⊕⊕◯◯ LOW	CRITICAL
Quality of life at 1 year (assessed with: EQ-5D (MID 0.074); Scale from: 0 (dead) to 1 (full health))												
1	randomised trials	serious [a,c]	not serious	not serious	serious [b]	none	34	37	MD **0.19 higher** (0.05 higher to 0.32 higher)		⊕⊕◯◯ LOW	CRITICAL
Overall survival												
1	randomised trials	not serious	not serious	not serious	serious [d]	none	There were no significant differences between VATS-PP and talc pleurodesis in the overall survival of patients up to 9 years of follow-up: HR: 1.04 (CI95% 0.76 to 1.42); p=0.81; N=175 patients. The Hazard Ratio, stratified by EORTC prognostic risk (high or low) was similar. Median survival was 13.1 month (IQR 7.3 to 20.3) in the VATS-PP and 13.5 (IQR 7.3 to 21.1) in the talc pleurodesis group.				⊕⊕⊕◯ MODERATE	CRITICAL
Overall survival at 6 months												
1	randomised trials	not serious	not serious	not serious	serious [d]	none	68/87 (78.2%)	70/88 (79.5%)	**RR 0.98** (0.84 to 1.15)	**16 fewer per 1.000** (from 127 fewer to 119 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Overall survival at 1 year												
1	randomised trials	not serious	not serious	not serious	serious [d]	none	45/87 (51.7%)	50/88 (56.8%)	**RR 0.91** (0.69 to 1.20)	**51 fewer per 1.000** (from 176 fewer to 114 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Biomarkers : simulations

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VATS partial pleurectomy	talc pleurodesis	Relative (95% CI)	Absolute (95% CI)		
Post-operative morbidity (serious adverse events)												
1	randomised trials	serious [a]	not serious	not serious	serious [d]	none	13/78 (16.7%)	8/73 (11.0%)	**RR 1.52** (0.67 to 3.46)	**57 more per 1.000** (from 36 fewer to 270 more)	⊕⊕◯◯ LOW	CRITICAL
Number of patients with pleural effusion resolution at 1 year												
1	randomised trials	serious [c]	not serious	not serious	serious [d]	none	23/33 (69.7%)	27/35 (77.1%)	**RR 0.90** (0.68 to 1.21)	**77 fewer per 1.000** (from 247 fewer to 162 more)	⊕⊕◯◯ LOW	CRITICAL
Number of patients with pleural effusion resolution at 6 months												
1	randomised trials	not serious	not serious	not serious	serious [e]	none	41/53 (77.4%)	31/54 (57.4%)	**RR 1.35** (1.03 to 1.77)	**201 more per 1.000** (from 17 more to 442 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Number of patients with pleural effusion resolution at 3 months												
1	randomised trials	not serious	not serious	not serious	serious [d]	none	36/60 (60.0%)	37/62 (59.7%)	**RR 1.01** (0.75 to 1.34)	**6 more per 1.000** (from 149 fewer to 203 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Number of patients with pleural effusion resolution at 1 month												
1	randomised trials	not serious	not serious	serious [f]	not serious	none	41/69 (59.4%)	25/68 (36.8%)	**RR 1.62** (1.12 to 2.33)	**228 more per 1.000** (from 44 more to 489 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Operative mortality												
1	randomised trials	not serious	not serious	not serious	very serious [g]	none	There were one death (at least possibly related to treatment) in the VAT-PP group and none in the talc pleurodesis group.				⊕⊕◯◯ LOW	IMPORTANT
Hospital length of stay												

Biomarkers : simulations

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VATS partial pleurectomy	talc pleurodesis	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [h]	not serious	none	Median hospital stay after the procedure was 7 days (IQR 5 to 11) for the VAT-PP group and 3 days (IQR 2 to 5) for the talc pleurodesis group; p<0.0001)				⨁⨁◯◯ LOW	IMPORTANT
Incidence of "seeding" tract metastases - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Time to treatment failure - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
30 days mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
90 days mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Time to disease progression - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. Open trial design might have influenced the assessment of this outcome
b. 95%CI crosses the MID threshold and ranges from non relevant effect to important benefit. Low number of patients - optimal information size not met
c. Large number of patients lost of follow-up
d. Limited number of events; 95%CI points to a substantial benefit or harm
e. Limited number of events; 95%CI points to a substantial benefit or negligible effect

Biomarkers : simulations

f. Short follow-up. Results at one month does not seem to replicate at longer follow-up

g. One single event

h. Hospital length of stay is an administrative outcome much influenced by each institution policy and not directly related to patient important outcomes

EQ-5D MID from: Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005 Aug;14(6):1523-32.

Table S15: Should radical surgery (including extrapleural pneumonectomy or pneumonectomy/decortication) be used as in patients with symptomatic malignant pleural mesothelioma?

Bibliography: 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 Oncology 2011; 12: 763-772

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	surgery (EPP: extra-pleural pneumectomy)	non surgical approach	Relative (95% CI)	Absolute (95% CI)		
Quality of life at 6 months (assessed with: EORTC, QLQ-C30 and QLQ-LC13)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	Median quality-of-life scores seemed to be lower for the EPP group (58.3) than the no EPP group (66.7)				⊕◯◯◯ VERY LOW	CRITICAL
Quality of life at 1 year (assessed with: EORTC, QLQ-C30 and QLQ-LC13)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	Median quality-of-life scores seemed to be lower for the EPP group (41.7) than the no EPP group (70.8)				⊕◯◯◯ VERY LOW	CRITICAL
Deaths at the end of follow-up (median 24.7 months)												
1	randomised trials	serious [c]	not serious	not serious	serious [d]	none	17/24 (70.8%)	13/26 (50.0%)	**RR 1.42** (0.89 to 2.25)	**210 more per 1.000** (from 55 fewer to 625 more)	⊕⊕◯◯ LOW	CRITICAL
Overall survival												
1	randomised trials	serious [c]	not serious	not serious	serious [e]	none	The overall survival favored the non EPP group (non surgical approach): HR 2.75 (1.21 to 6.26) adjusted for sex, histological subtype, stage, and age at randomisation.				⊕⊕◯◯ LOW	CRITICAL
12-months survival												
1	randomised trials	serious [c]	not serious	not serious	serious [d]	none	EPP (surgery) 52.2% (95% CI 30.5 to 70); no EPP (non surgical approach) 73.1% (51.7 to 86.2) (difference 18.0%, from –1.8 to 43.9)				⊕⊕◯◯ LOW	IMPORTANT

Biomarkers : simulations

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	surgery (EPP: extra-pleural pneumectomy)	non surgical approach	Relative (95% CI)	Absolute (95% CI)		
12-months recurrence-free survival												
1	randomised trials	serious [c]	not serious	not serious	serious [e]	none	EPP (surgery) 34.8% (95% CI 16.6 to 53.7); no EPP (non surgical approach) 42.3% (23.5 to 60)				⊕⊕◯◯ LOW	IMPORTANT
Operative mortality												
1	randomised trials	serious [c]	not serious	not serious	not serious [f]	none	There were 3 deaths among 19 patients receiving the EPP surgical approach. Non surgical approach is not linked to this adverse outcome.				⊕⊕⊕◯ MODERATE	IMPORTANT
Post-operative morbidity												
1	randomised trials	serious [c]	not serious	not serious	not serious [f]	none	There were 11 post-opertive complications among 16 patients completing the EPP surgical approach. Non surgical approach is not linked to this adverse outcome.				⊕⊕⊕◯ MODERATE	IMPORTANT
Location of recurrence - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
30 days mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
90 days mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Hospital length of stay - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Biomarkers : simulations

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

a. Open trial design might have influenced the assessment of this outcome. Feasibility trial not reaching the pre-specified sample size. Significant number of patients did not complete the questionnaires

b. 95%CI for differences only provided in figures, wide intervals

c. Feasibility trial not reaching the pre-specified sample size

d. Limited number of events; 95%CI points to a substantial benefit or harm

e. Limited number of patients and events

f. Although the number of patients and events is very limited, this adverse outcome is only related to surgical approach

g. Hospital length of stay is an administrative outcome much influenced by each institution policy and not directly related to patient important outcomes

Table S16: Should radical surgery (including extrapleural pneumonectomy or pneumonectomy/decortication) be used as in patients with symptomatic malignant pleural mesothelioma?

Bibliography: Bovolato P, Casadio C, Bille A et al. Does surgery improve survival of patients with malignant pleural mesothelioma?: a multicenter retrospective analysis of 1365 consecutive patients. Journal of Thoracic Oncology 2014; 9: 390-396

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery (EPP: extra-pleural pneumectomy or PD: pneumectomy/decortication)	non surgical approach	Relative (95% CI)	Absolute (95% CI)		
Survival												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	Non-surgical approach: median 11.7 months (range 10.5 to 12.5); PD: median 20.5 months (95%CI 18.2 to 23.1); EPP median 18.8 months (95%CI 17.2 to 20.9)				⊕◯◯◯ VERY LOW	CRITICAL
Overall mortality												
1	observational studies	not serious [c]	not serious	not serious	not serious	none	Against non-surgical approach the overall mortality in PD was HR 0.69 (95%CI 0.55 to 0.86) and in EPP was HR 0.77 (95%CI 0.64 to 0.93).				⊕⊕◯◯ LOW	CRITICAL
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
30 days mortality												
1	observational studies	serious [a]	not serious	not serious	not serious [d]	none	PD: 2.6% (5/202); EPP 4,1% (12/301)				⊕◯◯◯ VERY LOW	IMPORTANT
90 days mortality												
1	observational studies	serious [a]	not serious	not serious	not serious [d]	none	PD: 6% (12/202); EPP 6.9% (21/301)				⊕◯◯◯ VERY LOW	IMPORTANT
Post-operative complications												

Biomarkers : simulations

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery (EPP: extra-pleural pneumectomy or PD: pneumectomy/decortication)	non surgical approach	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious [e]	none	PD 10.4% (21/202); EPP: 21.6% (65/301)				⊕◯◯◯ VERY LOW	IMPORTANT
Length of hospital stay - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Time to tumor progression - recurrence free survival - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Location of recurrence - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. Retrospective cohort; not adjusted for this outcome
b. Treatment group differences not provided, although results point to a benefit for surgical options individual estimates have a large 95%CI
c. Retrospective cohort but Adjusted to key risk factors for this outcome
d. Although the number of events is low, this short-term mortality is only linked to surgical approaches
e. Although the number of events is low, this adverse outcome is only linked to surgical approaches

Biomarkers : simulations

Table S17: Should radiotherapy be used to prevent procedure-tract methastases (drain site parietal seeding) in patients with malignant pleural mesothelioma?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy for the prevention of procedure-tract metastases	control or deferred radiotherapy	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [b]	none	102	101	**HR 1.00** (0.68 to 1.47)		⊕⊕⊕◯ MODERATE	IMPORTANT
Disease (metastasis) free survival												
1 [2]	randomised trials	not serious	not serious [a]	not serious	Serious [b]	none	31	30	**HR 1.28** (0.29 to 5.65)		⊕⊕⊕◯ MODERATE	IMPORTANT
Number of patients with tract-metastasis												
5 [1,2,3,4,5]	randomised trials	not serious	serious [c]	not serious	Serious [b]	none	24/367 (9.9%)	40/370 (16.6%)	**OR 0.64** (0.27 to 1.51)	**4 fewer per 100** (from 8 fewer to 5 more)	⊕⊕◯◯ LOW	CRITICAL
Time to tract metastasis development												
2 [1,2]	randomised trials	not serious	not serious [d]	not serious	Very serious [e]	none	Clive 2016 does not show differences between groups in median time to tract metastasis (days) between immediate and delayed RT: 179 (IQR 126-221) vs. 224 (IQR 136-285), respectively. In O'Rourke 2007 the time from procedure until development of tract metastasis was 2.4 months in RT group and 6.4 months in control group (p=0.8).				⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

Explanations

Biomarkers : simulations

a. Single study
b. Wide 95%CI that includes the possibility of a large benefit or harm
c. Large variability among individual studies effects estimates
d. Both effect estimates seem to point a benefit of RT or immediate RT
e. The effect estimates cannot be pooled and the range of potential real effect (95%CI) is unknown.

References

1. Clive AO, Taylor H,Dobson L,Wilson P,de Winton E,Panakis N,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 oncology; 2016.
2. O'Rourke N, Garcia JC,Paul J ,Lawless C,McMenemin R ,Hill J. A randomised controlled trial of intervention site radiotherapy in malignant pleural mesothelioma. Radiotherapy and Oncology; 2007.
3. Bydder S, Phillips M,Joseph DJ,Cameron F,Spry NA,DeMelker Y,Musk AW. A randomised trial of single-dose radiotherapy to prevent procedure tract metastasis by malignant mesothelioma. British Journal of Cancer; 2004.
4. Boutin C, Rey F,Viallat JR. Prevention of Malignant Seeding After Invasive Diagnostic Procedures in Patients With Pleural Mesothelioma. A Randomized Trial of Local Radiotherapy. Chest; 1995.
5. Bayman N, Appel W, Ashcroft L et al. Prophylactic irradiation of tracts (PIT) in patients with pleural mesothelioma: results of a multicentre phase III trial. Lung Cancer (Amsterdam, Netherlands) 2018; 115: S30

Table S18: Should adjuvant post-operative radiotherapy be used in patients with malignant pleural mesothelioma?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post-operative RT	no RT	Relative (95% CI)	Absolute (95% CI)		
Overall survival time from treatment initiation												
1 [1]	randomised trials	not serious	not serious [a]	not serious [b]	serious [c]	None	27	27	19·3 months (11·5–21·8) in the radiotherapy group 20·8 b months (95% CI 14·4–27·8) in the no radiotherapy group	MD **1.5 months fewer** (11.12 fewer to 8.12 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Locoregional relapse free survival time from treatment initiation												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [c]	None	27	27	12·2 months (9·5–14·8) in the radiotherapy group 11 months (95% CI 7·5–13·5) in the no radiotherapy group	MD **1.2 months fewer** (5.41 fewer to 3.01 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Locoregional relapse free survival time from surgery												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [c]	None	27	27	9·4 months (6·5–11·9) in the radiotherapy group 7.6 months (95% CI 4·5–10·7) in the no radiotherapy group	MD **1.8 months more** (2.25 fewer to 5.85 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Quality of life

1 [1]	randomised trials	not serious	not serious [a]	not serious	very serious [d]	None	27	27	Quality of life, psychological and physical symptom distress and activity level impairment improved over time in patients not receiving radiotherapy. Patients receiving radiotherapy reported rather stable scores in these domains, except for their activity level, which worsened up to 4 weeks after randomisation, but recovered to baseline scores thereafter. No changes in the scores for the overall evaluation of quality life in both groups up to week 14 after randomisation	⊕⊕◯◯ LOW	CRITICAL

Adverse events

1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [e]	None	27	27	Grade 3 toxic effects induced by radiotherapy were nausea or vomiting, oesophagitis, fatigue, weight loss, dyspnoea, diarrhoea, and increased alkaline phosphatase concentration. One patient had grade 4 radiation pneumonitis of the contralateral lung and one patient died of a complicated pneumonia during radiotherapy.	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

Explanations

a. Single study
b. The overall median survival of 20 months in part 2 was less than expected when compared with—often retrospective—clinical reports. This result might partly be explained by the inclusion of patients with worse prognosis in this study.
c. Wide 95%CI that includes appreciable harm or benefit
d. No comparative numerical results given.
e. Low number of patients. Although the results refers only to radiotherapy group, in those patients not receiving radiotherapy these adverse events are not expected.

References

1. Stahel RA, Riesterer O, Xyrafas A, Opitz I, Beyeler M, Ochsenbein 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

Biomarkers : simulations

Table S19: Should first line chemotherapy consisting of platinum alone or in combination with pemetrexed be used in patients with malignant pleural mesothelioma?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**FIRST LINE Conventional chemotherapy with Cisplatin and Carboplatin**	**Carboplatin and pemetrexed**	**Relative (95% CI)**	**Absolute (95% CI)**		
Response rate (complete and partial response)												
1 [1]	randomised trials	serious [a]	not serious [b]	not serious	serious [c]	none	15/19 (78.9%)	10/21 (47.6%)	**RR 1.66** (1.00 to 2.75)	**314 more per 1.000** (from 0 fewer to 833 more)	⊕⊕◯◯ LOW	CRITICAL
Overall survival												
1 [1]	randomised trials	Not serious	not serious [b]	not serious	Very serious [d]	none	11/19 (57.9%)	9/21 (42.9%)	**RR 1.35** (0.72 to 2.52)	**150 more per 1.000** (from 120 fewer to 651 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Not blinded assessment for a data adjudication (subjective) outcome.
b. Single study
c. Low number of events; wide 95%CI includes no effect or large benefit
d. Very low number of events from underpowered study; 95%CI includes either large benefit or harm

References

1. Habib EE, Fahmy ES.Chemotherapy management of malignant pleural mesothelioma: a phase II study comparing two popular chemotherapy regimens. Clin Transl Oncol. 2013;15(11):965-8.

Table S20: Should bevacizumab be added to first line standard chemotherapy in patients with malignant pleural mesothelioma?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FIRST LINE with bevacizumab added to standard CT	standard CT (alone or with placebo)	Relative (95% CI)	Absolute (95% CI)		
Median time to progression												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	223	225	-	MD **1.9 months more** (0.71 more to 3.09 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Time to progression survival												
1 [1]	randomised trials	not serious	not serious [b]	not serious	serious [c]	none	-/223	-/225	**HR 0.61** (0.50 to 0.74)		⊕⊕⊕◯ MODERATE	CRITICAL
Median overall survival												
1 [1]	randomised trials	not serious	not serious	not serious	serious [c]	none	223	225	-	MD **2.7 months more** (1.18 fewer to 6.58 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Overall survival												
1 [1]	randomised trials	not serious	not serious	not serious	serious [c]	none	-/223	-/225	**HR 0.77** (0.62 to 0.96)		⊕⊕⊕◯ MODERATE	CRITICAL
Number of patients discontinued due to adverse events												
1 [1]	randomised trials	not serious	not serious [e]	not serious	not serious	none	53/222 (23.9%)	13/224 (5.8%)	**RR 4.11** (2.31 to 7.33)	**180 more per 1.000** (from 76 more to 367 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Number of patients discontinued due to progression												

Biomarkers : simulations

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FIRST LINE with bevacizumab added to standard CT	standard CT (alone or with placebo)	Relative (95% CI)	Absolute (95% CI)		
1 [1]	randomised trials	not serious	not serious [d]	not serious	not serious	none	137/222 (61.7%)	189/224 (84.4%)	**RR 0.73** (0.65 to 0.82)	**228 fewer per 1.000** (from 295 fewer to 152 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Number of patients with grade 3-4 adverse events												
1 [1]	randomised trials	not serious	not serious	not serious	serious [c]	none	158/222 (71.2%)	139/224 (62.1%)	**RR 1.15** (1.00 to 1.31)	**93 more per 1.000** (from 0 fewer to 192 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Number of patients with neutropenia												
1 [1]	randomised trials	not serious	not serious	not serious	not serious	none	173/222 (77.9%)	177/224 (79.0%)	**RR 0.99** (0.89 to 1.09)	**8 fewer per 1.000** (from 87 fewer to 71 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. Wide 95%CI does not exclude no effect or benefit
b. Large heterogeneity mostly due to the small study. Both studies show a beneficial effect but larger study points to significant reduction in time to progression.
c. Wide 95%CI does not exclude harm or benefit
e. Single study

References

1. Zalcman G, Mazieres J,Margery J,Greillier L,Audigier-Valette C,Moro-Sibilot D,Molinier O,Corre R,Monnet I,Gounant V,Rivière F,Janicot H,Gervais R,Locher C,Milleron B,Tran Q,Lebitasy MP,Morin F,Creveuil C,Parienti JJ,Scherpereel A, (IFCT)., French,Cooperative,Thoracic,Intergroup. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial.. Lancet; 2016.

Table S21: Should targeted therapies (including axitinib, nintedanib, defactinib, thalidomeide,CBP501) be added to first line standard chemotherapy in patients with malignant pleural mesothelioma?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FIRST LINE Targeted therapies	placebo	Relative (95% CI)	Absolute (95% CI)		
Median time to progression - First line												
2 [1,2,3]	randomised trials	not serious	not serious	not serious [a,b,c]	serious [d,e]	none	54	34	-	MD **1.55 months more** (0.75 fewer to 3.86 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Median time to progression - Maintenance												
2 [4,5]	randomised trials	not serious	not serious	not serious [f,g]	not serious	none	284	281	-	MD **0.1 months more** (0.93 fewer to 1.13 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Time to progression survival - First line												
1 [2]	randomised trials	not serious	not serious	not serious [b]	serious [d,e]	none	-/44	-/43	**HR 0.56** (0.34 to 0.92)		⊕⊕⊕◯ MODERATE	CRITICAL
Time to progression survival - Maintenance												
1 [4]	randomised trials	not serious	not serious	not serious [f]	Serious [i]	none	-/111	-/110	**HR 0.95** (0.73 to 1.24)		⊕⊕⊕◯ MODERATE	CRITICAL
Median overall survival - First line												
2 [1,3]	randomised trials	not serious	serious [h]	not serious [a,c]	serious [e,i]	none	54	34	-	MD **0.49 months more** (4.99 fewer to 5.98 more)	⊕⊕◯◯ LOW	CRITICAL
Median overall survival - Maintenance												
2 [4,5]	randomised trials	not serious	serious [h]	not serious [f,g]	serious [j]	none	284	281	-	MD **1.79 months fewer** (5.02 fewer to 1.45 more)	⊕⊕◯◯ LOW	CRITICAL

Biomarkers : simulations

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FIRST LINE Targeted therapies	placebo	Relative (95% CI)	Absolute (95% CI)		
Overall survival - First line												
1 [2]	randomised trials	not serious	serious [h]	not serious [b]	serious [e,i]	none	-/54	-/34	**HR 0.77** (0.46 to 1.29)		⊕⊕◯◯ LOW	CRITICAL
Overall survival - Maintenance												
2 [4,5]	randomised trials	not serious	serious [h]	not serious [f,g]	serious [i]	none	-/284	-/281	**HR 1.12** (0.89 to 1.40)		⊕⊕◯◯ LOW	CRITICAL
Number of patients with partial response												
3 [1,2,3]	randomised trials	not serious	not serious	not serious [a,b,c]	serious [e,i]	none	42/97 (43.3%)	23/74 (31.1%)	**RR 1.42** (0.96 to 2.10)	**131 more per 1.000** (from 12 fewer to 342 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Number of patients with stable disease												
2 [1,3]	randomised trials	not serious	not serious	not serious [a,c]	serious [e,i]	none	21/53 (39.6%)	18/31 (58.1%)	**RR 0.69** (0.44 to 1.08)	**180 fewer per 1.000** (from 325 fewer to 46 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Number of patients with grade 3-4 adverse events - First line												
2 [2,3]	randomised trials	not serious	serious [k]	not serious [b,c]	serious [e,i]	none	56/84 (66.7%)	35/66 (53.0%)	**RR 1.23** (0.75 to 2.04)	**122 more per 1.000** (from 133 fewer to 552 more)	⊕⊕◯◯ LOW	CRITICAL
Number of patients with grade 3-4 adverse events - Maintenance												
1 [4]	randomised trials	not serious	not serious	not serious [f]	serious [i]	none	43/111 (38.7%)	31/110 (28.2%)	**RR 1.37** (0.94 to 2.01)	**104 more per 1.000** (from 17 fewer to 285 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Number of patients with any adverse event												

Biomarkers : simulations

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FIRST LINE Targeted therapies	placebo	Relative (95% CI)	Absolute (95% CI)		
1 [4]	randomised trials	not serious	not serious	not serious [f]	serious [i]	none	106/111 (95.5%)	89/110 (80.9%)	**RR 1.18** (1.07 to 1.30)	**146 more per 1.000** (from 57 more to 243 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Number of patients with neutropenia - First line

2 [1,2]	randomised trials	not serious	not serious	not serious [a,b]	serious [e,i]	none	38/64 (59.4%)	13/52 (25.0%)	**RR 2.38** (1.44 to 3.93)	**345 more per 1.000** (from 110 more to 733 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

Number of patients with neutropenia - Maintenance

1 [4]	randomised trials	not serious	not serious	not serious [f]	serious [e,i]	none	14/111 (12.6%)	10/110 (9.1%)	**RR 1.39** (0.64 to 2.99)	**35 more per 1.000** (from 33 fewer to 181 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. Axitinib
b. Nintedanib
c. CBP501
d. 95%CI includes either a substantial benefit or no effect.
e. Limited number of patients included
f. Thalidomide
g. Defactinib
h. Median overall survival values have not a normal distribution and are not consistent with time-to-event data
i. 95%CI includes a substantial benefit or harm.
j. 95%CI includes a substantial harm or no effect
k. Large variability among individual studies effect estimates

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Table S22: Should immunotherapies (including immune checkpoint inhibitor tremelimumab and vorinostat) be used as salvage therapy in patients with malignant pleural mesothelioma who failed to first-line standard chemotherpy?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SALVAGE therapies**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Overall survival												
2 [1,2]	randomised trials	not serious	not serious	not serious	serious [a]	none	711	521	**HR 0.95** (0.84 to 1.08)		⊕⊕⊕◯ MODERATE	CRITICAL
Overall mortality (at data cutoff)												
1 [1]	randomised trials	not serious	not serious [b]	not serious	serious [a]	none	307/382 (80.4%)	154/189 (81.5%)	**RR 0.99** (0.91 to 1.07)	**8 fewer per 1.000** (from 57 more to 73 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Median overall survival												
2 [1,2]	randomised trials	not serious	not serious	not serious	serious [c]	none	Tremelimumab: 7.7 months (95%CI 6.8-8.9); Placebo: 7.3 months (95%CI 5.9-8.7) (571 patients). Vorinostat 30.7 weeks (95%CI 26.7-36.1); placebo: 27.1 weeks (95%CI 23.1-31.9) (661 patients)				⊕⊕⊕◯ MODERATE	CRITICAL
Number of patients with partial response												
1 [1]	randomised trials	not serious	not serious [b]	not serious	serious [d]	none	17/382 (4.5%)	2/189 (1.1%)	**RR 4.21** (0.98 to 18.01)	**34 more per 1.000** (from 0 fewer to 180 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Number of patients with stable disease												
1 [1]	randomised trials	not serious	not serious [b]	not serious	serious [a]		104/382 (27.2%)	41/189 (21.7%)	**RR 1.26** (0.91 to 1.72)	**56 more per 1.000** (from 20 fewer to 156 more)	-	IMPORTANT

Biomarkers : simulations

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SALVAGE therapies	placebo	Relative (95% CI)	Absolute (95% CI)		
Number of patients with grade >3 adverse events												
2 [1,2]	randomised trials	not serious	not serious	not serious	serious [e]	none	433/711 (60.9%)	260/518 (50.2%)	**RR 1.21** (1.01 to 1.46)	**105 more per 1.000** (from 5 more to 231 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Number of patients with adverse events of any grade												
1 [1]	randomised trials	not serious	not serious [b]	not serious	not serious	none	364/380 (95.8%)	179/189 (94.7%)	**RR 1.01** (0.97 to 1.05)	**9 more per 1.000** (from 28 fewer to 47 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Number of patients discontinued due to adverse events												
2 [1,2]	randomised trials	not serious	not serious	not serious	not serious	none	124/709 (17.5%)	12/521 (2.3%)	**RR 5.75** (3.24 to 10.20)	**109 more per 1.000** (from 52 more to 212 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Number of patients discontinued due to progression												
2 [1,2]	randomised trials	not serious	not serious	not serious	serious [e]	none	438/709 (61.8%)	411/521 (78.9%)	**RR 0.81** (0.64 to 1.02)	**150 fewer per 1.000** (from 16 more to 284 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. 95%CI include an appreciable benefit or harm
b. Single study
c. Results could not be aggregated but due to the high variability in point estimates it cannot be excluded a benefit or harm with the intervention compared to placebo
d. Very low number of patients; 95%CI includes an appreciable benefit or no effect
e. 95%CI includes appreciable benefit or no effect

References

Biomarkers : simulations

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Detailed PICO questions

	Should partial pleurectomy compared to talc pleurodesis be used as palliative surgery in patients with symptomatic malignant pleural mesothelioma?
Patients	Patients with symptomatic (short of breath) malignant pleural mesothelioma patients
Intervention	Partial pleurectomy
Comparison	Talc pleurodesis
Outcomes	Overall survival Postoperative morbidity Time to progression Time to treatment failure (effusion control) Health-related quality of life (QOL) Hospital length of stay Operative mortality 30 day mortality 90 day mortality "Seeding" – tract metastases
Type of studies	Systematic reviews of randomized controlled trials Randomized controlled trials Non randomized prospective trials

	Should radical surgery (including extrapleural pneumonectomy or pneumonectomy/decortication) be used as in patients with symptomatic malignant pleural mesothelioma?
Patients	Patients with symptomatic (short of breath) malignant pleural mesothelioma patients
Intervention	Radical surgery including extrapleural pneumonectomy or pneumonectomy/decortication
Comparison	Treatment approach NOT including radical surgery
Outcomes	Overall survival Postoperative morbidity Time to progression Time to treatment failure (effusion control) Health-related quality of life (QOL) Hospital length of stay Operative mortality 30 day mortality 90 day mortality "Seeding" – tract metastases
Type of studies	Systematic reviews of randomized controlled trials Randomized controlled trials Non randomized prospective trials

	Should radiotherapy be used for pain relief in patients with malignant pleural mesothelioma?
Patients	Patients with malignant pleural mesothelioma with persistent pain (regardless of adequate management of pain with analgesia)
Intervention	Radiotherapy of the painful area
Comparison	NO radiotherapy
Outcomes	Response rate (measured as pain reduction) Health-related quality of life (QOL) Adverse events
Type of studies	Systematic reviews of randomized controlled trials Randomized controlled trials Non randomized prospective trials

	Should radiotherapy be used to prevent procedure-tract methastases (drain site parietal seeding) in patients with malignant pleural mesothelioma?
Patients	Patients with malignant pleural mesothelioma after pleural intervention (thoracic surgery, large bore chest drain, indwelling pleural catheter or local anaesthetic thoracoscopy)
Intervention	Radiotherapy
Comparison	NO adjuvant radiotherapy
Outcomes	Overall survival Progression-free survival Number of patients with tract metastasis Health-related quality of life (QOL) Adverse events
Type of studies	Systematic reviews of randomized controlled trials Randomized controlled trials Non randomized prospective trials

	Should adjuvant post-operative radiotherapy be used in patients with malignant pleural mesothelioma?
Patients	Patients with resected malignant pleural mesothelioma, after pleurectomy, or EPP or any type of surgery except diagnostic thoracoscopy
Intervention	Postoperative Radiotherapy
Comparison	NO adjuvant radiotherapy
Outcomes	Overall survival Progression-free survival Time to progression Time to treatment failure Health-related quality of life (QOL) Adverse events
Type of studies	Systematic reviews of randomized controlled trials Randomized controlled trials Non randomized prospective trials

	Should first line chemotherapy consisting of platinum alone or in combination with pemetrexed be used in patients with malignant pleural mesothelioma?
Patients	Patients with malignant pleural mesothelioma
Intervention	First line chemotherapy consisting of platinum alone (cisplatin or carboplatin)
Comparison	Carboplatin and pemetrexed
Outcomes	Overall survival Progression-free survival Response rate Time to progression/ treatment failure Health-related quality of life (QOL) Adverse events
Type of studies	Systematic reviews of randomized controlled trials Randomized controlled trials

Biomarkers : simulations

	Should bevacizumab be added to first line standard chemotherapy in patients with malignant pleural mesothelioma?
Patients	Patients with malignant pleural mesothelioma: - Not previously treated with chemotherapy. - Fit for chemotherapy
Intervention	Bevacizumab be added to first line standard chemotherapy
Comparison	standard chemotherapy
Outcomes	Overall survival Progression-free survival Response rate Time to progression/ treatment failure Health-related quality of life (QOL) Adverse events
Type of studies	Systematic reviews of randomized controlled trials Randomized controlled trials

	Should targeted therapies (including axitinib, nintedanib, defactinib, thalidomeide,CBP501) be added to first line standard chemotherapy in patients with malignant pleural mesothelioma?
Patients	Patients with malignant pleural mesothelioma: - Not previously treated with chemotherapy. - Fit for chemotherapy
Intervention	Targeted therapies added to first line standard chemotherapy: Axitinib, nintedanib, defactinib, thalidomeide,CBP501
Comparison	standard chemotherapy
Outcomes	Overall survival Progression-free survival Response rate Time to progression/ treatment failure Health-related quality of life (QOL) Adverse events
Type of studies	Systematic reviews of randomized controlled trials Randomized controlled trials

	Should immunotherapies (including immune checkpoint inhibitor tremelimumab and vorinostat) be used as salvage therapy in patients with malignant pleural mesothelioma who failed to first-line standard chemotherpy?
Patients	Patients with malignant pleural mesothelioma who previously failed to first line chemotherapy .
Intervention	Immunotherapies: - Including immune checkpoint inhibitor tremelimumab and vorinostat
Comparison	Placebo
Outcomes	Overall survival Progression-free survival Response rate Time to progression/ treatment failure Health-related quality of life (QOL) Adverse events
Type of studies	Systematic reviews of randomized controlled trials Randomized controlled trials

	Should multimodal therapy approach (combining more than one method of cancer treatment: surgery, chemotherapy, radiation therapy) compared to chemotherapy alone be used in patients with malignant pleural mesothelioma?
Patients	Patients with resectable malignant pleural mesothelioma who are eligible for neoadjuvant therapy and or adjuvant treatment (good performance status, low tumor burden and early stage disease)
Intervention	Multimodal therapy approach: - Combining more than one method of cancer treatment: surgery, chemotherapy, radiation therapy)
Comparison	No treatment combination (surgery, chemotherapy or radiation therapy alone)
Outcomes	Overall survival Progression-free survival Response rate Time to progression/ treatment failure Health-related quality of life (QOL) Adverse events
Type of studies	Systematic reviews of randomized controlled trials Randomized controlled trials

Implications of strong and weak recommendations for different users of guidelines		
	Strong Recommendation	Weak Recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Appendix.

QUESTIONS (*PICO)	**RECOMMENDATIONS**
EPIDEMIOLOGY	
MPM screening	***Research priority:*** *The relationship between PP and MPM should be ascertained in large international epidemiological studies. The effectiveness of CT scan screening in the population exposed to asbestos should be determined in well-designed clinical trials.*
Biomarkers for MPM	***Research priority:*** *Routine determination of previously proposed biomarkers in MPM have currently no validated role for diagnosis, prognosis or clinical follow up (disease monitoring) . Thus further research into the role of biomarkers in these goals is required and highly encouraged.*
STAGING	
Clinical staging	***Research priority:*** *Prospective data collection about the measurement of tumour thickness or volume is to be encouraged.*
Pre-treatment staging investigations	***Research priority:*** *The prospective use of volumetric assessment software should be encouraged.*
Which other prognostic factors are of importance?	***Research priority:*** *The use of the Brims score is encouraged in routine, and other scores as part of clinical trials*
SURGERY*	
Should partial pleurectomy compared to talc pleurodesis be used as a palliative procedure in patients with symptomatic MPM?	*We recommend talc poudrage via thoracoscopy to control a recurrent MPM effusion as the first choice to achieve pleurodesis in patients with expanded lungs (strong recommendation, low quality of evidence).* *We suggest palliative VATS partial pleurectomy for selected patients fit enough to undergo surgery to obtain pleural effusion control in symptomatic patients who cannot benefit from (or after failure of) chemical pleurodesis or indwelling catheter (weak recommendation, low quality of evidence)***.**
Should radical surgery (including extrapleural pneumonectomy or pneumonectomy/decortication) be used in patients with MPM?	***Research priority:*** *patients considered for radical surgery should be either included in prospective, randomized, controlled clinical trials or in national/international surgical registries.* *Remark: Surgery may be appropriate for carefully and highly*

	selected MPM patients. This would usually be eP/D rather than EPP because of its lower comparative respiratory postoperative morbidity and preservation of quality of life, performed in centres of excellence and as part of multimodality treatment. Patients with sarcomatoid or sarcomatoid predominant histology, N2 disease (8th edition TNM staging system) and/or stage IV should not be considered for radical surgery unless in the context of research. However, as no single prognostic factor influences treatment allocation then prognostic scores encompassing several prognostic factors should be preferred (see Staging/allocation chapter).
RADIOTHERAPY*	
Should radiotherapy be used for pain relief in patients with MPM?	*We suggest that palliative radiotherapy for pain relief should be considered in cases of painful sites of disease caused by local infiltration of normal structures (weak recommendation, low quality evidence).*
Should radiotherapy be used to prevent procedure-tract methastases (drain site parietal seeding) in patients with MPM?	*We do not recommend prophylactic drain site radiotherapy in routine clinical care (strong recommendation, moderate quality evidence).*
Should adjuvant post-operative radiotherapy be used in patients with MPM?	***Research priority:*** *Radiotherapy after pleurectomy ± decortication or after EPP should be only considered within the context of clinical trials and/or included in national/international surgical registries.*
MEDICAL TREATMENT*	
Should first line chemotherapy consisting of platinum in combination with pemetrexed be used in patients with MPM?	*we recommend first line combination chemotherapy consisting of platinum and pemetrexed (with folic acid and vitamin B12 supplementation) in patients fit for chemotherapy (good performance status, PS ECOG 0-2, no contra-indications) (strong recommendation, low quality evidence)* ***Research priority:*** *Patients demonstrating prolonged symptomatic and objective response with first line pemetrexed-based chemotherapy may be treated again with the same regimen in the event of recurrence. In the other cases, inclusion of the patients in clinical trials is highly encouraged.*
Should targeted therapies be added to first line standard chemotherapy in patients with MPM? Should bevacizumab be added to first line standard chemotherapy in patients with MPM?	*We suggest bevacizumab may be proposed in combination with cisplatin/pemetrexed as first line treatment in patients fit for bevazucimab and cisplatin but not for macroscopic complete resection (weak recommendation, moderate quality of evidence).*

Should immunotherapy be used as salvage therapy in patients with MPM who failed first-line standard chemotherapy?	***Research priority:*** *Novel insights in immunotherapy are promising but need further development and results from ongoing or planned phase III trials before to draw any clear recommendation for their use in routine. Inclusion of patients in these trials is highly recommended.*
MULTIMODAL TREATMENT*	
Should a multimodal therapy approach (combining more than one method of cancer treatment: surgery, chemotherapy, radiation therapy) compared to chemotherapy alone be used in patients with MPM?	***Research priority:*** *We still recommend that patients who are considered candidates for a multimodal approach should be adequately informed of its challenges and referred to expert centers in order to be included in a prospective (randomized) clinical trial or registred in a large institutional database.*
TREATMENT ALLOCATION of MPM	
	Research priority: *Current and future scores suggested for patients treatment allocation, always decided by MPM expert multidisciplinary board, would require prospective validation by multicenter studies.*
FOLLOW-UP of MPM PATIENTS	
What should be the follow-up of a patient after active treatment of MPM?	***Research priority:*** *The role of a periodic follow-up with imaging (chest-abdominal CT scan, MRI or PET) should be assessed in clinical trials.* *Remarks: Monitoring of disease progression should be guided by signs and symptoms occurring during clinical follow up. However, in addition to clinical follow-up, and waiting for further evidence from clinical trials, the TF group suggest a chest-abdominal CT scan every 3 to 6 months after active treatment of MPM patients.*