MESOTHELIOMA

CHI Formulary Development Project

مجلس الضمان الصحي
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Abbreviations

AUC	Area Under the Curve
ASCO	American Society of Clinical Oncology
CADTH	Canadian Agency for Drugs and Technologies in Health
CC	Completeness of Cytoreduction
CHI	Council of Health Insurance
CrCl	Creatinine Clearance
CRS	Cytoreductive Surgery
CT	Computed Tomography
DPeM	Diffuse Malignant Peritoneal Mesothelioma
EPP	Extrapleural Pneumonectomy
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
HAS	Haute Autorite de Sante
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
HR	Hazard Ratio
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IDF	Insurance Drug Formulary
IMRT	Intensity-Modulated Radiation Therapy
IQWIG	Institute for Quality and Efficiency in Health Care
ICI	Immune Checkpoint Inhibitor
IP	Intraperitoneal
IV	Intravenous
KSA	Kingdom of Saudi Arabia
MPM	Malignant Pleural Mesothelioma
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
OS	Overall Survival
PBAC	Pharmaceutical Benefits Advisory Committee
P/D	Pleurectomy/Decortication
PD-L1	Programed Cell Death-Ligand 1
PeM	Peritoneal Mesothelioma
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PS	Performance Status

QALY	Quality-Adjusted Life Years
RT	Radiation Therapy
SFDA	Saudi Food and Drug Authority
TNM	Tumor, Node, Metastasis
WDPMT	Well-Differentiated Papillary Mesothelial Tumor

Executive Summary

Mesothelioma is a rare cancer originating in mesothelial surfaces of the pleura and other sites that is estimated to occur in approximately 3500 people in the United States every year[1]. Malignant pleural mesothelioma (MPM) is the most common type, representing approximately 85% of the cases. Mesothelioma can also occur in the lining of other sites, such as the peritoneum (approximately 15%), pericardium, and tunica vaginalis testis[2]. MPM occurs mainly in older males (median age at diagnosis, 72 years) who have been exposed to asbestos, although death occurs decades after exposure (approximately 32 years later [range, 13–70 years])[3–6].

Clinical presentation – Most patients with MPM present with the gradual onset of nonspecific symptoms such as chest pain, dyspnea, cough, hoarseness, or dysphagia, which occur in the setting of extensive intrathoracic disease. Chest imaging typically shows unilateral pleural thickening and pleural effusion[7]. Cigarette smoking is not a risk factor for the development of MPM[8]. As for peritoneal mesothelioma (PeM), the majority of cases present with diffuse peritoneal involvement. Common complaints include abdominal distention and/or increasing abdominal girth, abdominal pain, nausea, anorexia, and weight loss. Rarely, patients present with a paraneoplastic syndrome (fever, thrombocytosis, hypoglycemia)[9].

Diagnostic evaluation – Initial evaluation of patients with suspected MPM includes computed tomography (CT) of the chest with contrast, thoracentesis of any existing pleural effusion, and closed pleural biopsy. However, if insufficient tissue is acquired to make a diagnosis, surgical intervention via video-assisted thoracoscopic biopsy or open thoracotomy should be pursued[10]. As for PeM, the imaging patterns and features are shown equally well on CT and magnetic resonance imaging. The pattern of involvement is usually diffuse and widespread involvement of the peritoneal cavity with tumor infiltration and irregular/nodular thickening of the peritoneum in a sheet-like fashion, usually with moderate to extensive ascites[11].

Diagnosis – The diagnosis of mesothelioma is established by morphologic and immunohistochemical features of a cytologic or surgical specimen[12].

Staging evaluation – For diagnosed cases of pleural mesothelioma, integrated positron emission tomography (PET) with CT (PET-CT) should be obtained as the initial staging assessment. For patients in whom imaging suggests resectable disease, extended surgical staging is pursued prior to definitive surgery. Specifically, this includes laparoscopy with peritoneal lavage to detect subdiaphragmatic involvement, followed by mediastinoscopy[13]. There is no uniformly accepted staging system for PeM. Given the very low risk of extra-abdominal spread, a radiographic staging workup is generally not needed in the absence of symptoms.

Prognosis – MPM is difficult to treat, because most patients have advanced disease at presentation. The prognosis of patients with MPM is poor. Median overall survival is approximately 1 year after diagnosis of MPM, and 5-year overall survival is about 10%; cure is rare[14–17].

Treatment

Patients with mesothelioma are managed by a multidisciplinary team with experience in mesothelioma[2,18–23].

A. Malignant Pleural Mesothelioma (MPM)

a. Surgery

Surgery is recommended for certain patients with clinical stage I to IIIA MPM and epithelioid histology. Surgery may be considered for certain patients with early-stage MPM who have biphasic histology. It is important to note that cases like biphasic or sarcomatous histology should still be discussed in MDT where surgery may be considered. However, surgery is generally not an option for those with stage IIIB or IV MPM regardless of histology. It is essential that patients receive a careful assessment before surgery is performed[2,19,20,22,23].

Surgical resection for patients with MPM can include either:

1. Pleurectomy/decortication (P/D; also known as total pleurectomy, lung-sparing surgery), which is complete removal of the involved pleura and all gross tumor with or without en-bloc resection of the pericardium and/or diaphragm; or
2. Extrapleural pneumonectomy (EPP), which is en-bloc resection of the involved pleura, lung, ipsilateral diaphragm, and often the pericardium.

Extended P/D refers to the resection of the diaphragm and pericardium in addition to total pleurectomy. Mediastinal nodal dissection is recommended in patients having either P/D or EPP; at least 3 nodal stations should be obtained[2,19,20,22,23].

b. Systemic Therapy

Chemotherapy is recommended as part of a **multimodality regimen** for patients with **medically operable** MPM. Patients with **medically operable stage I to IIIA MPM** can receive chemotherapy either before or after surgery (Recommendation Level A, Evidence Level II) [2,19,20,22,23].

Systemic therapy alone is recommended for patients with[2,19,20,22,23]:

1. **Stage IIIB or IV MPM (PS 0–2)** regardless of histology;
2. Those with **sarcomatoid** or **biphasic** histology, regardless of clinical stage; or
3. **Medically inoperable** stages I to IV MPM, or those who refuse surgery (Recommendation Level A, Evidence Level II).

All of the regimens recommended for MPM can also be used for **malignant peritoneal mesothelioma**, **pericardial mesothelioma**, and **tunica vaginalis testis** mesothelioma[2,19,20,22,23].

b.1 Medically Operable MPM

Preoperative (induction) chemotherapy with **pemetrexed plus (cisplatin or carboplatin)** is recommended for eligible patients with *resectable MPM* (Recommendation Level A, Evidence Level II). **Postoperative chemotherapy** is also recommended if patients *have not received induction chemotherapy* (Recommendation Level A, Evidence Level II)[2,19,20,22,23].

b.2 Medically Inoperable MPM

b.2.1 First-Line Therapy

- **Nivolumab plus ipilimumab** immunotherapy is recommended for eligible patients with unresectable MPM based on clinical trial data and the FDA approval (Recommendation Level A, Evidence Level II). It is the **preferred** option for patients with **biphasic or sarcomatoid histology**[2,19,20,22,23]. In the Checkmate 743 trial, survival benefit was clear in all mesotheliomas; The forest plot showed a higher overall survival in non-epitheloid mesothreliomas[2].
    - Testing for PD-L1 is not required for prescribing nivolumab for therapy for patients with MPM.
    - Immune-related adverse events, such as pneumonitis, may occur with nivolumab plus ipilimumab. Intravenous high-dose corticosteroids should be administered based on the severity of the reaction for patients with immune-mediated adverse events.
    - Nivolumab plus ipilimumab should be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated.
    - Ipilimumab can also cause immune-mediated adverse events such as hepatitis and endocrinopathies[2].
- **Cisplatin/Pemetrexed** is recommended for patients with MPM based on clinical trial data and the FDA approval (Recommendation Level A, Evidence Level I). It's a **preferred** first-line treatment option in patients with **epitheliod histology**[2,19,20,22,23].
    - **Carboplatin/Pemetrexed** is an alternative treatment option based on clinical trial data in patients who are not eligible for cisplatin (Recommendation Level A, Evidence Level II)[2].
- **Cisplatin/Pemetrexed/Bevacizumab** followed by **Bevacizumab maintenance** is a treatment option for bevacizumab-eligible patients with unresectable MPM regardless of histology (Recommendation Level A,

Evidence Level I). It's also a **preferred** first-line treatment option in patients with **epitheliod histology**[2,19,20,22,23].

- Contraindications to bevacizumab include uncontrolled hypertension, risk for bleeding or clotting, and substantial cardiovascular morbidity.
- An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
- **Bevacizumab** can be added to carboplatin/pemetrexed with or without maintenance bevacizumab as a first-line therapy option for patients with unresectable MPM (Recommendation Level A, Evidence Level I)[2,19,20,22,23].

- **Gemcitabine/cisplatin** is a treatment option for eligible patients with unresectable MPM (Recommendation Level A, Evidence Level II)[2,19,20,22,23].
- Other first-line options include **pemetrexed** or **vinorelbine** for patients who are *not candidates* for platinum-based combination therapy (Recommendation Level A, Evidence Level I)[2,19,20,22,23].

A recent phase 3, open label, randomized controlled trial examined the role of pembrolizumab as an addition to chemotherapy in untreated advanced pleural mesothelioma. Patients aged 18 years or older with ECOG performance status of 0 or 1 were randomly assigned (1:1) to intravenous chemotherapy (cisplatin [75 mg/m2] or carboplatin [area under the concentration-time curve 5–6 mg/mL per min] with pemetrexed 500 mg/m2, every 3 weeks for up to 6 cycles), with or without intravenous pembrolizumab 200 mg every 3 weeks (up to 2 years). The primary endpoint was overall survival in all randomly assigned patients; safety was assessed in all randomly assigned patients who received at least one dose of study therapy. Overall survival (OS) was significantly longer with pembrolizumab (median overall survival 17.3 months [95% CI 14.4–21.3] with pembrolizumab vs. 16.1 months [13.1–18.2] with chemotherapy alone, hazard ratio for death 0.79; 95% CI 0.64–0.98, two-sided p=0.0324). The 3-year overall survival rate was 25% with pembrolizumab and 17% with chemotherapy alone. Adverse events related to study treatment of grade 3 or 4 occurred in 27% of patients in the pembrolizumab group and 15% of patients in the chemotherapy alone group. Hospital admissions for serious adverse events related to one or more study drugs were reported in 18% of patients in the pembrolizumab group and 6% of patients in the chemotherapy alone group. Grade 5 adverse events related to one or more drugs occurred in two patients on the pembrolizumab group and one patient in the chemotherapy alone group[24].

b.2.2 Subsequent Systemic Therapy

The following are recommended subsequent therapy options for patients with MPM (if not administered first line)[2,19,20,22,23]:

1. **Pemetrexed** (Recommendation Level A, Evidence Level I). It's a preferred subsequent treatment option if immunotherapy was given in first line; or
2. **Pemetrexed/(Cisplatin or Carboplatin) ± Bevacizumab** (Recommendation Level A, Evidence Level I). It's a preferred subsequent treatment option if immunotherapy was given in first line; or
3. **Nivolumab** with (or without) **Ipilimumab** (Recommendation Level A, Evidence Level II). It's the preferred subsequent treatment option if chemotherapy was given in first line.

Other subsequent chemotherapy options include[2,19,20,22,23]:

1. **Rechallenging** with **pemetrexed-based regimens** if patients had a good, sustained response to first-line therapy (Recommendation Level A, Evidence Level II);
2. **Vinorelbine** (Recommendation Level A, Evidence Level II); or
3. **Gemcitabine ± Ramucirumab** (Recommendation Level A, Evidence Level II)[2]

c. Radiation Therapy (RT)

In patients with MPM, RT can be used as part of a multimodality regimen; however, RT alone is not recommended for treatment. RT can also be used as palliative therapy for relief of chest pain, bronchial or esophageal obstruction, or other symptomatic sites associated with MPM, such as metastases in bone or in the brain[2,19,20,22,23].

The dose of radiation should be based on the purpose of treatment. The most appropriate timing of delivering RT (i.e., after surgical intervention, with [or without] chemotherapy) should be discussed with a multidisciplinary team. After EPP, adjuvant hemithoracic RT may reduce the local recurrence rate. Patients are candidates for RT if they have good PS, pulmonary function, and kidney function[2,19,20,22,23].

In patients with limited or no resection of disease (i.e., in the setting of an intact lung), high-dose conventional RT to the entire hemithorax has not been shown to improve survival and is associated with significant toxicity[2].

- Hemithoracic pleural Intensity-modulated radiation therapy (IMRT) can be considered following induction chemotherapy and P/D in certain patients with MPM if done in centers with expertise in this technique.
- Prophylactic RT is not routinely recommended to prevent instrument-tract recurrence after pleural intervention based on the SMART trial.
- Hemithoracic pleural IMRT is not recommended after EPP.

B. Peritoneal Mesothelioma (PeM)

Treatment options for patients with diffuse PeM include **surgery** and/or **systemic therapy**[2,18,21].

- For patients being considered for surgery, a laparoscopy is recommended to determine candidacy for **complete cytoreduction**[2].
    - The goal of surgery is complete gross cytoreduction of the tumor. The goal of CRS is "macroscopic complete resection"—in other words, removal of ALL visible or palpable tumors (CC-0)[2].
    - A near complete cytoreduction with <2.5 mm visible residual disease (CC-1) is also acceptable for epithelioid mesothelioma subtype, as a large multi-institutional study suggests <2% change in 5-year overall survival and unchanged median OS for epithelioid peritoneal mesothelioma undergoing CC-1 compared to CC-0.2 In cases where this is not possible, palliative surgery and/or HIPEC can be considered if associated with minimal morbidity. Otherwise, surgery should be aborted/not offered[2].
    - Complete cytoreduction frequently requires a total parietal peritonectomy, including visceral resections when necessary to achieve complete cytoreduction[2].
- Select patients with medically operable diffuse PeM and good performance status (PS) are candidates for multimodality therapy, including those with epithelioid histology and unicavitary disease.
- **Systemic therapy** is recommended for patients with **diffuse PeM** who are not eligible for or refuse surgery. Best supportive care is recommended for patients with a PS of 3 to 4, based on well-designed retrospective case-control or cohort studies.
- **Radiation therapy** is not recommended as a primary therapy for PeM but can be used selectively for **palliation**.

Treatment options for patients with peritoneal inclusion cyst or well-differentiated papillary mesothelial tumor (WDPMT) include[2,18,21]:

1. Observation with imaging surveillance for those with asymptomatic and noninvasive disease; or
2. Cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) for those who have symptomatic, recurrent, or microinvasive disease.

There are no phase 3 randomized trials to determine the best treatment for patients with PeM because it is so rare, although there are a few clinical trials. Because PeM and pleural mesothelioma are similar, systemic therapy recommendations for PeM are based on extrapolating data from clinical trials in

pleural mesothelioma; recommendations are also based on clinical trials in PeM, and on the expertise of the NCCN panel members[2].

a. Surgery and Intraperitoneal Chemotherapy

Cytoreductive surgery (CRS) and **Hyperthermic intraperitoneal chemotherapy** (HIPEC) are possible for eligible patients with PeM. Appropriate patients should be evaluated by surgeons, medical oncologists, and diagnostic imaging specialists to assess if they are candidates for multimodality treatment[2,18,21].

Complete cytoreduction and HIPEC are recommended for patients with **unicavitary PeM** and **epithelioid histology** who are medically operable if a complete cytoreduction is achievable. **Perioperative systemic therapy** should be considered if patients have **high-risk features** (such as Ki-67 >9%, nodal metastases, high tumor burden [peritoneal cancer index >17]), completeness of cytoreduction (CC) > 1, biphasic disease, or bicavitary disease). Although measuring the Ki-67 index is not routinely recommended at diagnosis, it may be useful for helping to define high-risk features. After perioperative therapy, patients may be eligible for CRS and HIPEC[2,18,21].

Intraperitoneal chemotherapy regimens and stratified as per below[2,18,21]:

1. Cisplatin plus doxorubicin;
2. Cisplatin;
3. Carboplatin; or
4. Cisplatin plus mitomycin

Monotherapy mitomycin regimens are useful in certain circumstances[2].

b. Systemic Therapy

Systemic therapy alone is recommended for patients with a PS of 0 to 2 and diffuse PeM, including those who[2,18,21]:

1. who are medically **inoperable**, for whom a complete CRS cannot be achieved, or who refuse surgery;
2. with **bicavitary disease** regardless of histology and stage;
3. with **sarcomatoid** or **biphasic histology** regardless of stage; or
4. with **recurrence** after previous CRS and HIPEC.

Surgery may be considered in select patients with bicavitary disease or low-volume biphasic disease. The systemic therapy regimens are also recommended for eligible patients with pleural mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma[2].

Preferred first-line systemic therapy regimens for eligible patients with **PeM** and **epithelioid histology** who are not eligible for surgery and are[2,18,21]:

1. **Pemetrexed/Cisplatin/Bevacizumab** (Recommendation Level A, Evidence Level II)

2. **Pemetrexed/cisplatin** (Recommendation Level A, Evidence Level II)
3. **Nivolumab/Ipilimumab** (Recommendation Level A, Evidence Level II)

The **preferred first-line** systemic therapy regimens for eligible patients with **PeM** and **biphasic or sarcomatoid histology** who are not eligible for surgery is **nivolumab plus ipilimumab** (Recommendation Level A, Evidence Level II)[2,18,21].

The following are other recommended regimens for biphasic or sarcomatoid histology[2,18,21]:

1. **Pemetrexed/Cisplatin/Bevacizumab** (Recommendation Level A, Evidence Level II)
2. **Pemetrexed/Cisplatin** (Recommendation Level A, Evidence Level II)

The following regimens are useful in certain circumstances (all histologies)[2,18,21]:

1. **Gemcitabine/Cisplatin** (Recommendation Level A, Evidence Level II)
2. **Pemetrexed** (Recommendation Level A, Evidence Level II)
3. **Vinorelbine** (Recommendation Level A, Evidence Level II).

Carboplatin is recommended if patients are **not candidates for cisplatin**, regardless of histology (Recommendation Level A, Evidence Level II)[2].

Preferred subsequent (second-line and beyond) **systemic therapy** regimens for eligible patients with **PeM**, regardless of histology, if they were not given first line are[2,18,21]:

1. **Pemetrexed/Cisplatin/Bevacizumab** (Recommendation Level A, Evidence Level II)
2. **Pemetrexed/Cisplatin** (Recommendation Level A, Evidence Level II)
3. **Pemetrexed** (Recommendation Level A, Evidence Level II)
4. **Nivolumab/Ipilimumab** (Recommendation Level A, Evidence Level II)

However, pemetrexed regimens may be given again as subsequent systemic therapy if a good sustained response was obtained when the initial chemotherapy was interrupted[2].

The following are other recommended subsequent therapy regimens[2,18,21]:

1. **Atezolizumab plus Bevacizumab** (Recommendation Level A, Evidence Level II). Atezolizumab plus bevacizumab should only be considered as subsequent therapy if patients have not previously been treated with ICIs[2]. This recommendation is based on a phase 2 trial data:
    - It assessed atezolizumab plus bevacizumab as subsequent therapy for 20 patients with advanced and unresectable PeM who had progressed on or were intolerant to pemetrexed plus platinum chemotherapy. Most patients had epithelioid histology (90%); The

response rate was 40% (8/20; 95% CI, 19%–64%). Overall survival at 1 year was 85% (95% CI, 60%–95%)[2].

2. **Vinorelbine** (Recommendation Level A, Evidence Level II)
3. **Gemcitabine** (Recommendation Level A, Evidence Level II)

Although about 50% of patients with PeM have positive programed cell death-ligand 1 (PD-L1) expression levels, PD-L1 testing is not required before using ICIs. ICIs are associated with unique immune-mediated adverse events, such as endocrine disorders, that are not seen with traditional cytotoxic chemotherapy; therefore, health care providers should be aware of the spectrum of potential immune-mediated adverse events, know how to manage the adverse events, and educate their patients about possible side effects. Atezolizumab, nivolumab, or ipilimumab should be discontinued for patients with severe or life-threatening pneumonitis or myocarditis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated-mediated adverse events when indicated[2].

With 35 cases registered in 2021, mesothelioma ranked **31st in cancer incidence in the Kingdom of Saudi Arabia** and accounted for 0.13% of all newly diagnosed cases reported[25]. Mesothelioma was correlated with **28 deaths in 2020**, with a **5-year prevalence of 49 cases (0.14 cases per 100,000)**.

This report compiles all clinical and economic evidence related to mesothelioma according to the relevant sources. The ultimate objective of issuing mesothelioma guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to mesothelioma patients in Saudi Arabia**. The main focus of the review was on Saudi, North American and European guidelines issued within the last five years in addition to recent systematic reviews and meta-analyses.

The management of mesothelioma involves a **multidisciplinary approach** and greatly differs based on the stage of the disease[2,18,23]. There are currently **multiple treatment regimen options for the management of mesothelioma on the global market**. KSA has access to all of them. Section 2 provides a full description of each with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of mesothelioma. Section 3 lists the key recommendations synthesis for mesothelioma treatment.

Major recommendations for suggested drug therapies for mesothelioma are summarized in Tables 1 and 2 below[2,18,23]:

Table 1. Treatment Options for the Management of Pleural Mesothelioma

Management of Pleural Mesothelioma				
Medication/ Protocol	**Indication**	**Line of Therapy**	**Recommendation**	**Evidence**
Cisplatin	First and second-line treatment of pleural mesothelioma (preferred for Epithelioid histology)	**1st** **2nd**	A A	I II
Carboplatin	First and second-line treatment of pleural mesothelioma in patients not candidates for cisplatin therapy (preferred for Epithelioid histology)	**1st, 2nd**	A	II
Pemetrexed	First and second-line treatment of pleural mesothelioma (preferred for Epithelioid histology)	**1st, 2nd**	A	I
Bevacizumab	First and second-line treatment of mesothelioma (preferred for Epithelioid histology)	**1st** **2nd**	A A	I II
Nivolumab	First and second-line treatment of mesothelioma (preferred for Biphasic or Sarcomatoid histology)	**1st** **2nd**	A A	I II
Ipilimumab	First and second-line treatment of pleural mesothelioma (preferred for Biphasic or Sarcomatoid histology)	**1st** **2nd**	A A	I II
Gemcitabine	First and second-line treatment of pleural mesothelioma	**1st, 2nd**	A	II
Virorelbine	First and second-line treatment of pleural mesothelioma	**1st, 2nd**	A	II
Ramucirumab	Second-line treatment of pleural mesothelioma	**2nd**	A	II

Table 2. Treatment Options for the Management of Peritoneal Mesothelioma

Management of Peritoneal Mesothelioma				
Medication/ Protocol	**Indication**	**Line of Therapy**	**Recommendation**	**Evidence**
Cisplatin	First and second-line treatment of peritoneal mesothelioma (preferred for Epithelioid histology) First-line treatment of PeM as part of HIPEC regimens	**1st, 2nd**	A	II
Carboplatin	First and second-line treatment of peritoneal mesothelioma in patients not candidates for cisplatin therapy (preferred for Epithelioid histology) First-line treatment of PeM as part of HIPEC regimens	**1st, 2nd**	A	II
Doxorubicin	First-line treatment of PeM as part of HIPEC regimens	**1st**	A	II
Pemetrexed	First and second-line treatment of peritoneal mesothelioma (preferred for Epithelioid histology)	**1st, 2nd**	A	II
Bevacizumab	First and second-line treatment of peritoneal mesothelioma (preferred for Epithelioid histology)	**1st, 2nd**	A	II
Nivolumab	First and second-line treatment of peritoneal mesothelioma (preferred for Epitheliod, Biphasic or Sarcomatoid histology)	**1st, 2nd**	A	II
Ipilimumab	First and second-line treatment of peritoneal mesothelioma (preferred	**1st, 2nd**	A	II

	for Biphasic or Sarcomatoid histology)			
Gemcitabine	First and second-line treatment of peritoneal mesothelioma	**1st, 2nd**	A	II
Virorelbine	First and second-line treatment of peritoneal mesothelioma	**1st, 2nd**	A	II
Atezolizumab	Second-line treatment of peritoneal mesothelioma	**2nd**	A	II

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in mesothelioma were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

HTA recommendations were found for the immunotherapy combination Nivolumab + Ipilimumab as well as for Pemetrexed in malignant pleural mesothelioma (cf. section 2).

The Nivolumab plus Ipilimumab immunotherapy combination has received positive recommendations from HAS, NICE, CADTH, and IQWIG in the malignant pleural mesothelioma indication:

- **HAS recommends the reimbursement** of nivolumab + ipilimumab in the **first-line treatment of adult patients with unresectable malignant pleural mesothelioma**, citing a **therapeutic improvement** compared to pemetrexed and platinum-based chemotherapy, a **substantial clinical benefit**, and a **minor clinical added value (CAV IV)**.
- **NICE** guidance **recommends** nivolumab + ipilimimab as an option for **untreated unresectable malignant pleural mesothelioma** in adults with performance status 0-1, citing **improved overall survival and progression free survival compared with chemotherapy**, and **meeting NICE's criteria for being a life-extending treatment at the end of life**. The **cost-effectiveness estimates** for nivolumab plus ipilimumab were **within the range that NICE normally considers an acceptable use of NHS resources**.
- CADTH recommends that **nivolumab plus ipilimumab should be reimbursed** by public drug plans for the treatment of **malignant pleural mesothelioma** to treat patients who have **not received prior systemic treatment** for MPM and who have good performance status. The committee cites that nivolumab plus ipilimumab **improved overall**

survival in adults with unresectable MPM with good performance status and who had not received prior MPM treatment. However, nivolumab plus ipilimumab **is not considered cost-effective** at a willingness to pay of $50,000 per QALY for the indicated population relative to currently reimbursed alternatives. **A price reduction of at least 72% is needed** for both nivolumab and ipilimumab to ensure this combination is cost-effective at a $50,000 per QALY threshold.

- For **IQWIG**, the added benefit of the combination nivolumab + ipilimumab depends on the **tumor histology**. In patients with **epithelioid** tumor histology the **added benefit of the combination is not proven**, while in patients with **non-epithelioid** tumor histology there's an **indication of considerable added benefit**. This aligns with the NCCN preferred treatment recommendations stated for each histological subtype.

Pemetrexed has received positive recommendations from HAS and NICE in the malignant pleural mesothelioma indication:

- **HAS recommends the reimbursement** of pemetrexed, citing a **substantial actual benefit** and **moderate clinical added value** in **first-line treatment of unresectable malignant pleural mesothelioma**.
- **NICE** on the other hand **recommends pemetrexed** as a treatment option for **malignant pleural mesothelioma** only in people who have a World Health Organization (WHO) performance status of 0 or 1, who are considered to have **advanced disease** and for whom **surgical resection is considered inappropriate.** The results of the EMPHACIS trial suggest that **pemetrexed plus cisplatin** confers a **survival benefit of approximately 3 months** compared with **cisplatin alone**, in addition to **advantages** in terms of 1**-year survival, median time to progressive disease, tumor response rate and quality of life.** The economic analyses indicate an incre**mental cost per QALY gained of greater than £60,000** when pemetrexed plus cisplatin was compared with cisplatin alone in the fully supplemented population. Pemetrexed plus cisplatin, when compared with cisplatin alone, appears to have **lower ICERs in patients with advanced disease and/or good performance status**.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

To date, no clinical guidelines have been published by Saudi bodies for the management of mesothelioma.

1.2 North American Guidelines

1.2.1 National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN) published its updated recommendations for the management of pleural and peritoneal mesothelioma in November 2023[2]. These recommendations are summarized in the sections below.

1.2.1.1 Pleural Mesothelioma (Version 1.2024)

Treatment options for patients with MPM include surgery, radiation therapy (RT), and/or systemic therapy. Most patients have advanced disease at presentation, and surgery is not recommended for these patients.

a. Staging

Patients who are not candidates for surgery only have clinical staging. It is difficult to clinically stage patients using CT, MRI, or PET/CT; therefore, patients who have surgery may be upstaged. Under-staging is common with PET/CT. However, PET/CT is useful for determining whether metastatic disease is present. Surgical staging is performed using the International Mesothelioma Interest Group (IMIG) TNM staging system, which was approved by the AJCC.

b. Surgery

Surgery is recommended as a component of combined modality therapy for certain patients with stage I to IIIA MPM who are medically operable. The NCCN Panel recommends surgery for certain patients with clinical stage I to IIIA MPM and epithelioid histology. Surgery may be considered for certain patients with early-stage MPM who have biphasic histology. However, surgery is generally not an option for those with stage IIIB or IV MPM regardless of histology. It is essential that patients receive a careful assessment before surgery is performed.

Surgical resection for patients with MPM can include either:

1. pleurectomy/decortication (P/D; also known as total pleurectomy, lung-sparing surgery), which is complete removal of the involved pleura and all gross tumor with or without en-bloc resection of the pericardium and/or diaphragm; or

2. extrapleural pneumonectomy (EPP), which is en-bloc resection of the involved pleura, lung, ipsilateral diaphragm, and often the pericardium.

Extended P/D refers to the resection of the diaphragm and pericardium in addition to total pleurectomy. Mediastinal nodal dissection is recommended in patients having either P/D or EPP; at least 3 nodal stations should be obtained.

c. Systemic Therapy

Chemotherapy is recommended as part of a multimodality regimen for patients with medically operable MPM. Patients with medically operable stage I to IIIA MPM can receive chemotherapy either before or after surgery. Systemic therapy alone is recommended for patients with:

1. Stage IIIB or IV MPM (PS 0–2) regardless of histology;
2. Those with sarcomatoid or biphasic histology, regardless of clinical stage; or
3. Medically inoperable stages I to IV MPM, or those who refuse surgery.

All of the regimens recommended for MPM can also be used for malignant peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.

c.1 Medically Operable MPM

Trimodality therapy—using chemotherapy, surgery, and hemithoracic RT—has been studied in patients with medically operable MPM. The NCCN Panel recommends preoperative (induction) chemotherapy with pemetrexed plus (cisplatin or carboplatin) for eligible patients with resectable MPM based on clinical trial results[2]. The panel also recommends postoperative chemotherapy if patients have not received induction chemotherapy.

c.2 Medically Inoperable MPM

First-Line Therapy

- The NCCN Panel recommends (category 1) **nivolumab plus ipilimumab** for eligible patients with unresectable MPM based on clinical trial data and the FDA approval[2]. Testing for PD-L1 is not required for prescribing nivolumab for therapy for patients with MPM. Immune-related adverse events, such as pneumonitis, may occur with nivolumab plus ipilimumab. Intravenous high-dose corticosteroids should be administered based on the severity of the reaction for patients with immune-mediated adverse events. Nivolumab plus ipilimumab should be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated. Ipilimumab can also cause immune-mediated adverse events such as hepatitis and endocrinopathies.
- NCCN Panel recommends **cisplatin/pemetrexed** (category 1) for patients with MPM based on clinical trial data and the FDA approval. The panel also

recommends **pemetrexed/carboplatin** (category 2A) based on clinical trial data. Carboplatin regimens are recommended for patients who are not eligible for cisplatin.

- The NCCN Panel recommends (category 1) **bevacizumab, cisplatin, and pemetrexed** followed by **maintenance bevacizumab** for bevacizumab-eligible patients with unresectable MPM regardless of histology based on clinical trial data. Contraindications to bevacizumab include uncontrolled hypertension, risk for bleeding or clotting, and substantial cardiovascular morbidity. An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
- The NCCN Panel recommends (category 2A) adding **bevacizumab** to carboplatin/pemetrexed with or without maintenance bevacizumab as a first-line therapy option for patients with unresectable MPM.
- The NCCN Panel recommends **gemcitabine/cisplatin** for eligible patients with unresectable MPM based on clinical trial data.
- Other first-line options recommended by NCCN include **pemetrexed** or **vinorelbine** for patients who are *not candidates* for platinum-based combination therapy.

The NCCN Panel recommends systemic therapy alone for patients with MPM and PS 0 to 2, including:

1. those who are medically inoperable or refuse surgery;
2. those with clinical stage IIIB to IV MPM, regardless of histology; or
3. those with sarcomatoid or biphasic histology, regardless of clinical stage.

The NCCN Panel has preference stratified the systemic therapy regimens and voted that the following regimens are preferred first-line therapy options for certain patients with unresectable MPM:

1. Pemetrexed plus (cisplatin or carboplatin) with or without bevacizumab; or
2. Nivolumab plus ipilimumab.

For the 2022 update (Version 1), the panel decided that the pemetrexed/platinum with or without bevacizumab regimens were preferred options. The panel voted that nivolumab plus ipilimumab is a preferred option for patients with biphasic or sarcomatoid histology and is also an option for patients with epithelioid histology.

The panel voted that the following regimens are useful in certain circumstances:

1. Gemcitabine/cisplatin;
2. Pemetrexed; or
3. Vinorelbine

Subsequent Systemic Therapy

The NCCN Panel recommends the following subsequent therapy options for patients with MPM if not administered first line:

1. **Pemetrexed** (category 1); or
2. **Nivolumab** with (or without) **Ipilimumab** (category 2A).

The panel decided that if immunotherapy was administered as first-line treatment, then combination **pemetrexed/platinum** regimens are subsequent therapy options (e.g., pemetrexed plus either cisplatin or carboplatin).

The NCCN Panel also recommends other subsequent chemotherapy options based on clinical trial data, including:

1. Rechallenging with pemetrexed-based regimens if patients had a good, sustained response to first-line therapy;
2. Vinorelbine; or
3. Gemcitabine.

For the 2022 update (Version 1), the NCCN Panel **deleted pembrolizumab** as a subsequent therapy option for patients with relapsed MPM based on updated clinical trial data. As previously mentioned, immune-related adverse events, such as pneumonitis, may occur with nivolumab with (or without) ipilimumab.

The NCCN Panel has preference stratified the systemic therapy regimens and voted that the following regimens are preferred subsequent therapy options for certain patients with MPM who have progressed on systemic therapy, including:

1. Pemetrexed if not given first line (category 1);
2. Rechallenging with pemetrexed-based regimens if good response with first-line therapy; or
3. Nivolumab with (or without) ipilimumab.

The panel voted that the following regimens are other recommended options: 1) vinorelbine; or 2) gemcitabine.

d. Radiation Therapy

It is very challenging to deliver RT accurately and safely to the entire pleural surface without damaging radiosensitive sites, such as the lung and heart, especially when the lungs are intact. In patients with MPM, RT can be used as part of a multimodality regimen; however, RT alone is not recommended for treatment. RT can also be used as palliative therapy for relief of chest pain, bronchial or esophageal obstruction, or other symptomatic sites associated with MPM, such as metastases in bone or in the brain.

The dose of radiation should be based on the purpose of treatment. The most appropriate timing of delivering RT (i.e., after surgical intervention, with [or without] chemotherapy) should be discussed with a multidisciplinary team. After

EPP, adjuvant hemithoracic RT may reduce the local recurrence rate. Patients are candidates for RT if they have good PS, pulmonary function, and kidney function.

In patients with limited or no resection of disease (i.e., in the setting of an intact lung), high-dose conventional RT to the entire hemithorax has not been shown to improve survival and is associated with significant toxicity.

- The NCCN Panel recommends that hemithoracic pleural IMRT can be considered following induction chemotherapy and P/D in certain patients with MPM if done in centers with expertise in this technique.
- The NCCN Panel does not routinely recommend prophylactic RT to prevent instrument-tract recurrence after pleural intervention based on the SMART trial.
- The NCCN Panel does not recommend hemithoracic pleural IMRT after EPP.

Table 3. Systemic Therapy Regimens for Pleural Mesothelioma (NCCN Guidelines)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Epithelioid Histology		
First-Line Therapy		
• Cisplatin + pemetrexed (category 1) • Cisplatin + pemetrexed + bevacizumab (category 1) • Nivolumab/ipilimumab (category 1)	N/A	• Cisplatin + gemcitabine • Pemetrexed • Vinorelbine
Subsequent-Line Therapy		
If chemotherapy used first-line: • Nivolumab ± ipilimumab *If immunotherapy used first-line:* • Cisplatin + pemetrexed • Cisplatin + pemetrexed + bevacizumab • Pemetrexed (category 1)	• Gemcitabine ± ramucirumab • Vinorelbine	N/A
Biphasic or Sarcomatoid Histology		

First-Line Therapy		
• Nivolumab/ipilimumab (category 1)	• Cisplatinc + pemetrexed (category 1) • Cisplatin + pemetrexed + bevacizumab (category 1)	• Cisplatinc + gemcitabine • Pemetrexed • Vinorelbine
Subsequent-Line Therapy		
If chemotherapy used first-line: • Nivolumab ± ipilimumab *If immunotherapy used first-line:* • Cisplatin+ pemetrexed • Cisplatin + pemetrexed + bevacizumab • Pemetrexed (category 1)	• Gemcitabine ± ramucirumab • Vinorelbine	N/A

All recommendations are considered Category 2A unless specified otherwise

1.2.1.2 Peritoneal Mesothelioma (Version 1.2024)

Treatment options for patients with diffuse PeM include surgery and/or systemic therapy[18].

Select patients with medically operable diffuse PeM and good performance status (PS) are candidates for multimodality therapy, including those with epithelioid histology and unicavitary disease.

Systemic therapy is recommended for patients with diffuse PeM who are not eligible for or refuse surgery. Best supportive care is recommended for patients with a PS of 3 to 4.

Radiation therapy is not recommended as a primary therapy for PeM but can be used selectively for palliation. Treatment options for patients with peritoneal inclusion cyst or WDPMT include:

1. observation with imaging surveillance for those with asymptomatic and noninvasive disease; or
2. CRS with or without HIPEC for those who have symptomatic, recurrent, or microinvasive disease.

There are no phase 3 randomized trials to determine the best treatment for patients with PeM because it is so rare, although there are a few clinical trials. Because PeM and pleural mesothelioma are similar, systemic therapy recommendations for PeM are based on extrapolating data from clinical trials in pleural mesothelioma; recommendations are also based on clinical trials in PeM, and on the expertise of the panel members.

c. Surgery and Intraperitoneal Chemotherapy

The NCCN Panel recommends CRS and HIPEC for eligible patients with PeM based on trials for PeM and pleural mesothelioma. Appropriate patients should be evaluated by surgeons, medical oncologists, and diagnostic imaging specialists to assess if they are candidates for multimodality treatment.

Complete cytoreduction and HIPEC are recommended for patients with unicavitary PeM and epithelioid histology who are medically operable if a complete cytoreduction is achievable. Perioperative systemic therapy should be considered if patients have high-risk features (such as Ki-67 >9%, nodal metastases, high tumor burden [peritoneal cancer index >17]), CC > 1, biphasic disease, or bicavitary disease).

Although measuring the Ki-67 index is not routinely recommended at diagnosis, it may be useful for helping to define high-risk features. After perioperative therapy, patients may be eligible for CRS and HIPEC. Systemic therapy alone is recommended for patients with PS 0 to 2 who are medically inoperable or refuse surgery. The NCCN Panel has preference stratified the intraperitoneal chemotherapy regimens and voted that the following regimens are preferred:

1. cisplatin plus doxorubicin;
2. cisplatin;
3. carboplatin; or
4. cisplatin plus mitomycin

The panel has voted that monotherapy mitomycin regimens are useful in certain circumstances.

d. Systemic Therapy

The NCCN Panel recommends systemic therapy alone for patients with a PS of 0 to 2 and diffuse PeM, including those:

1. who are medically inoperable, for whom a complete CRS cannot be achieved, or who refuse surgery;
2. with bicavitary disease regardless of histology and stage;
3. with sarcomatoid or biphasic histology regardless of stage; or
4. with recurrence after previous CRS and HIPEC.

Surgery may be considered in select patients with bicavitary disease or low-volume biphasic disease. The systemic therapy regimens are also recommended for eligible patients with pleural mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.

Although about 50% of patients with PeM have positive programed cell death-ligand 1 (PD-L1) expression levels, the NCCN Panel does not require PD-L1 testing before using ICIs based on clinical trial data. ICIs are associated with unique immune-mediated adverse events, such as endocrine disorders, that are not seen with traditional cytotoxic chemotherapy; therefore, health care providers should be aware of the spectrum of potential immune-mediated adverse events, know how to manage the adverse events, and educate their patients about possible side effects. Atezolizumab, nivolumab, or ipilimumab should be discontinued for patients with severe or life-threatening pneumonitis or myocarditis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated-mediated adverse events when indicated.

The NCCN Panel has preference stratified the first-line systemic therapy regimens for eligible patients with PeM and epithelioid histology who are not eligible for surgery and voted that the following regimens are preferred options:

1. pemetrexed plus cisplatin plus bevacizumab;
2. pemetrexed plus cisplatin; or
3. nivolumab plus ipilimumab.

Carboplatin is recommended if patients are not candidates for cisplatin, regardless of histology. The panel voted that the following regimens are useful in certain circumstances for eligible patients with PeM and epithelioid histology:

1. gemcitabine plus cisplatin;
2. pemetrexed; or
3. vinorelbine.

The NCCN Panel has preference stratified the first-line systemic therapy regimens for eligible patients with PeM and biphasic or sarcomatoid histology who are not eligible for surgery and voted that nivolumab plus ipilimumab is the preferred option.

The panel voted that the following are other recommended regimens:

1. pemetrexed plus cisplatin plus bevacizumab; or
2. pemetrexed plus cisplatin.

The panel voted that the following regimens are useful in certain circumstances:

1. gemcitabine plus cisplatin;
2. pemetrexed; or

3. vinorelbine.

Carboplatin is recommended if patients are not candidates for cisplatin, regardless of histology.

The NCCN Panel has also preference stratified the subsequent (second-line and beyond) systemic therapy regimens for eligible patients with PeM and voted that the following regimens are preferred, regardless of histology, if they were not given first line:

1. pemetrexed plus cisplatin plus bevacizumab;
2. pemetrexed plus cisplatin;
3. pemetrexed; or
4. nivolumab plus ipilimumab.

However, pemetrexed regimens may be given again as subsequent systemic therapy if a good sustained response was obtained when the initial chemotherapy was interrupted. The panel decided that the following are other recommended subsequent therapy regimens:

1. atezolizumab plus bevacizumab;
2. vinorelbine; or
3. gemcitabine.

For the 2023 update (Version 1), the NCCN Panel clarified that atezolizumab plus bevacizumab should only be considered as subsequent therapy if patients have not previously been treated with ICIs.

Table 4. Systemic Therapy Regimens for Peritoneal Mesothelioma (NCCN Guidelines)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Epithelioid Histology		
First-Line Therapy		
• Cisplatin + pemetrexed • Cisplatin + pemetrexed + bevacizumab • Nivolumab/ipilimumab	N/A	• Cisplatin + gemcitabine • Pemetrexed • Vinorelbine
Subsequent-Line Therapy		
If chemotherapy used first-line: • Nivolumab ± ipilimumab	• Atezolizumab + bevacizumab or • Gemcitabine or • Vinorelbine	N/A

If immunotherapy used first-line: • Cisplatin + pemetrexed • Cisplatin + pemetrexed + bevacizumab • Pemetrexed		
Biphasic or Sarcomatoid Histology		
First-Line Therapy		
• Nivolumab/ipilimumab	• Cisplatin + pemetrexed • Cisplatin + pemetrexed + bevacizumab	• Cisplatin + gemcitabine • Pemetrexed • Vinorelbine
Subsequent-Line Therapy		
If chemotherapy used first-line: • Nivolumab ± ipilimumab If immunotherapy used first-line: • Cisplatin+ pemetrexed • Cisplatin + pemetrexed + bevacizumab • Pemetrexed	• Atezolizumab + bevacizumab or • Gemcitabine or • Vinorelbine	N/A

All recommendations are considered Category 2A unless specified otherwise

1.2.2 American Society of Clinical Oncology (ASCO) Clinical Practice Guideline on the Treatment of Malignant Pleural Mesothelioma (2018)

In 2018, the American Society of Clinical Oncology (ASCO) published clinical guidelines to provide evidence-based recommendations to practicing physicians and others on the management of malignant pleural mesothelioma[19]. The main treatment recommendations are summarized in the following sections:

a. Chemotherapy

- Chemotherapy should be offered to patients with mesothelioma because it improves survival and quality of life (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

- In asymptomatic patients with epithelial histology and minimal pleural disease who are not surgical candidates, a trial of close observation may be offered prior to the initiation of chemotherapy (Type of recommendation: informal consensus; Strength of recommendation: moderate).
- Select patients with a poor performance status (PS 2) may be offered single-agent chemotherapy or palliative care alone. Patients with a PS of 3 or greater should receive palliative care (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).
- The recommended first-line chemotherapy for patients with mesothelioma is pemetrexed plus platinum. However, patients should also be offered the option of enrolling in a clinical trial (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong)
- The addition of bevacizumab to pemetrexed-based chemotherapy improves survival in select patients and therefore may be offered to patients with no contraindications to bevacizumab. The randomized clinical trial demonstrating benefit with bevacizumab used cisplatin/pemetrexed; data with carboplatin/pemetrexed plus bevacizumab are insufficient for a clear recommendation (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: moderate)
- Bevacizumab is not recommended for patients with PS 2, substantial cardiovascular comorbidity, uncontrolled hypertension, age > 75, bleeding or clotting risk, or other contraindications to bevacizumab (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- In patients who may not be able to tolerate cisplatin, carboplatin may be offered as a substitute for cisplatin (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- Retreatment with pemetrexed-based chemotherapy may be offered in pleural mesothelioma patients who achieved durable (> 6 months) disease control with first-line pemetrexed-based chemotherapy (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).
- Given the very limited activity of second-line chemotherapy in patients with mesothelioma, participation in clinical trials is recommended (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

- In patients for whom clinical trials are not an option, vinorelbine may be offered as second-line therapy (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).
- In asymptomatic patients with epithelial mesothelioma and a low disease burden who are not surgical candidates, a trial of expectant observation may be offered before initiation of systemic therapy (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).
- Front-line pemetrexed-based chemotherapy should be given for four to six cycles. For patients with stable or responding disease, a break from chemotherapy is recommended at that point (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).
- There is insufficient evidence to support the use of pemetrexed maintenance in mesothelioma patients, and thus it is not recommended (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: strong).

b. Surgical Cytoreduction

- In select patients with early-stage disease, it is strongly recommended that a maximal surgical cytoreduction should be performed (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- Maximal surgical cytoreduction as a single modality treatment is generally insufficient; additional antineoplastic treatment (chemotherapy and/or radiation therapy) should be administered. It is recommended that this treatment decision should be made with multidisciplinary input involving thoracic surgeons, pulmonologists, medical and radiation oncologists (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- Patients with transdiaphragmatic disease, multifocal chest wall invasion, or histologically confirmed contralateral mediastinal or supraclavicular lymph node involvement should undergo neoadjuvant treatment before consideration of maximal surgical cytoreduction. Contralateral (N3) or supraclavicular (N3) disease should be a contraindication to maximal surgical cytoreduction (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- Patients with histologically confirmed sarcomatoid mesothelioma should not be offered maximal surgical cytoreduction (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

- Patients with ipsilateral histologically confirmed mediastinal lymph node involvement should only undergo maximal surgical cytoreduction in the context of multimodality therapy (neoadjuvant or adjuvant chemotherapy). Optimally, these patients should be enrolled in clinical trials. (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- Maximal surgical cytoreduction involves either extrapleural pneumonectomy (EPP) or lung-sparing options (pleurectomy/decortication [P/D], extended P/D). When offering maximal surgical cytoreduction, lung-sparing options should be the first choice, due to decreased operative and long-term risk. EPP may be offered in highly selected patients when performed in centers of excellence (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- A maximal cytoreduction (either lung sparing or non–lung sparing) should only be considered in patients who meet specific preoperative cardiopulmonary functional criteria, have no evidence of extrathoracic disease, and are able to receive multimodality treatment (adjuvant or neoadjuvant) (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- In patients who have a symptomatic pleural effusion, who are PS 2 or greater, or in whom a maximal cytoreduction cannot be performed (due to disease extent or comorbid conditions), palliative approaches such as a tunneled permanent catheter placement or thoracoscopic exploration with partial resection and/or pleurodesis should be offered. In the latter case, additional biopsy to confirm pathologic diagnosis should be performed during the procedure. If the patient is being evaluated for investigational therapy, material for additional studies (e.g., molecular and/or immunologic profiling) should be obtained. (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- In patients who have a symptomatic pericardial effusion, percutaneous catheter drainage or pericardial window may be performed (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).
- Since surgical cytoreduction is not expected to yield an R0 resection, it is strongly recommended that multimodality therapy with chemotherapy and/or radiation therapy should be administered (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

- Chemotherapy may be given pre- or postoperatively in the context of multimodality treatment (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).
- Adjuvant radiation therapy may be associated with a decreased risk of local recurrence and may be offered to patients who have undergone maximal cytoreduction. Treatment is complex, and it is recommended that it should be delivered at experienced centers of excellence (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- In the context of multimodality treatment, four to six cycles of pemetrexed/platin-based chemotherapy may be administered pre- or postoperatively (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- Intracavitary therapies (chemotherapy or photodynamic therapy) may be administered safely in experienced centers of excellence, preferably in the context of a clinical trial. Their role in improving outcome is indeterminate (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).
- Tunneled pleural catheters are not recommended in patients who are candidates for maximal surgical cytoreduction, because of the risk of tumor implantation into the chest wall (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- In patients who are not candidates for maximal surgical cytoreduction, tunneled pleural catheters or pleurodesis (performed via chest tube or thoracoscopy) may be offered. As noted above, these procedures should be performed using the minimal number and size incisions. Multidisciplinary input including surgical consultation with a center of excellence should be sought to optimize management of a pleural effusion and for consideration of investigational intracavitary therapies (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

c. Radiation Therapy

- Prophylactic irradiation of intervention tracts should generally not be offered to patients to prevent tract recurrences (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: moderate).
- It is recommended that adjuvant radiation should be offered to patients who have resection of intervention tracts found to be histologically positive (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

- Radiation therapy should be offered as an effective treatment modality to palliate patients with symptomatic disease (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- It is recommended that standard dosing regimens used in other diseases be offered to patients with mesothelioma (8 Gy × one fraction, 4 Gy × five fractions, or 3 Gy × 10 fractions) (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- Radiation therapy may be offered to patients with localized asymptomatic recurrence. The dosing fractionation is dependent on the site and extent of disease and should be determined by the radiation oncologist in consultation with the patient (Type of recommendation: informal consensus; Strength of recommendation: moderate).
- Hemithoracic adjuvant radiation therapy may be offered to patients who undergo non–lung-sparing cytoreductive surgery (EPP), preferably in centers of excellence with experience in this modality for mesothelioma (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- Hemithoracic neo-adjuvant radiation therapy may be offered to patients who undergo non–lung-sparing cytoreductive surgery. This potentially toxic regimen remains experimental and should only be performed in highly experienced centers within the context of a clinical trial (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- Hemithoracic adjuvant intensity-modulated radiation therapy may be offered to patients who undergo lung-sparing cytoreductive surgery (P/D or EPD). This potentially toxic regimen should only be performed in highly experienced centers, preferably in the context of a clinical trial (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- Due to the potential for severe pulmonary toxicity, neoadjuvant radiation therapy is not recommended for patients who undergo lung-sparing surgical cytoreductive surgery (Type of recommendation: informal consensus; Strength of recommendation: strong).
- For palliative radiation therapy, electrons, 2D, 3D, and IMRT may be considered appropriate techniques depending on location of the treatment target and organs at risk (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- For adjuvant or neoadjuvant hemithoracic radiation therapy, 3D or IMRT may be offered, respecting guidelines of organs at risk. Proton therapy may be considered in centers with significant experience, preferably in the

context of a clinical trial (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

- It is recommended that standard dosimetric guidelines for organs at risk be used as established predictors of radiation toxicity (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

1.3 European Guidelines

1.3.1 European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Diagnosis, Treatment, and Follow-Up of Malignant Pleural Mesothelioma (2021)

The European Society for Medical Oncology (ESMO) released in 2021 clinical practice guidelines for diagnosis, treatment, and follow up of malignant pleural mesothelioma (MPM)[20]. The key recommendations of the guideline are outlined in the following sections.

a. Diagnosis and pathology/Molecular biology

The diagnosis and pathology recommendations for malignant pleural mesothelioma according to the ESMO guidelines are shown in table 5.

Table 5. Diagnosis and Pathology Recommendations for Malignant Pleural Mesothelioma (ESMO guidelines)

Recommendations	Strength
Diagnostic Procedures	
▪ Diagnostic procedures should encompass at least occupational history with emphasis on asbestos exposure and contrast-enhanced CT of the thorax and upper abdomen.	II, A
▪ In all patients who have a unilateral pleural thickening, with or without fluid and/or pleural plaques, efforts should be made to obtain a pathological specimen. Thoracoscopy is preferred.	II, A
▪ The role of screening of persons exposed to asbestos for early MPM diagnosis is uncertain.	IV, E
▪ Circulating tumor markers cannot adequately distinguish MPM.	II, D
Pathological Sampling	
▪ Effusion cytology for MPM definitive diagnosis remains controversial and biopsy is recommended especially for histological subtyping and if clinical trial participation is considered.	IV, B

▪ Biopsy sampling of at least three distant sites when feasible, with possible targeting of areas of interest via thoracoscopic imaging, is recommended for robust subtyping and grading.	IV, B
Pathological Classification	
▪ Mesotheliomas should be classified using the current WHO criteria, including major subtype and documentation of architectural patterns, grading of epithelioid subtypes and stromal and cytologic features that refine prognostication.	IV, A
▪ Epithelioid mesotheliomas should be graded as low or high grade, with this stratification used in ongoing and future trials and research.	IV, B
▪ A diagnosis of mesothelioma *in situ* (MIS) can be made in a multidisciplinary (clinical, imaging, morphological and molecular) setting, with molecular tests undertaken in validated laboratories.	IV, A
Use of IHC (Immunohistochemistry)	
▪ IHC is recommended for all primary diagnoses of MPM [IV, A].	IV, A
▪ For epithelioid subtype, at least two 'mesothelial' markers and at least two '(adeno)carcinoma' markers should be used.	V, A
▪ For sarcomatoid subtype, cytokeratin staining should be used.	V, A
▪ Loss of BAP1 and/or MTAP as surrogate for CDKN2A deletion aid the MPM diagnosis and are required as part of the multidisciplinary diagnosis of MIS, undertaken in a strictly validated setting.	IV, A

b. Staging and Risk assessment

The staging and risk assessment recommendations for malignant pleural mesothelioma according to the ESMO guidelines are shown in table 6.

Table 6. Staging and Risk Assessment Recommendations for Malignant Pleural Mesothelioma (ESMO Guidelines)

Recommendations	Strength
Staging and Risk Assessment	
▪ The 8th revision of the UICC TNM staging system should be used for clinical and pathological staging.	I, A
▪ Non-invasive staging for a patient fit to undergo active treatment should include contrast-enhanced CT of the chest including the upper abdomen.	III, B
▪ For patients considered for MCR, additional staging including PET-CT should be carried out.	III, B

▪ Pathological staging should be limited to MCR specimens with smaller specimens being clinically staged.	V, B

c. Management of malignant pleural mesothelioma

The treatment recommendations for patients with malignant pleural mesothelioma according to the ESMO guidelines are shown in table 7.

Table 7. Treatment Recommendations for Patients with Malignant Pleural Mesothelioma (ESMO Guidelines)

Recommendations	Strength
Role of Surgery	
▪ Surgery is recommended to obtain diagnostic samples of tumor tissue and to stage the patient, for palliation of pleural effusions when chest tube drainage is not successful and to obtain diagnostic samples of tumor tissue and to stage the patient.	II, A
▪ Talc poudrage via thoracoscopy remains the first surgical procedure of choice for pleurodesis over video-assisted thoracic surgery partial pleurectomy.	I, A
▪ Macroscopic complete resection in combination with other modalities is recommended in selected MPM patients, to be carried out at experienced centers and to be discussed with a multidisciplinary team involving thoracic surgeons, pulmonologists, medical and radiation oncologists.	III, C
▪ Extended pleural decortication (EPD) is a lung-preserving procedure and is preferred over extrapleural pneumonectomy (EPP).	III, B
First-line Systemic Therapy	
▪ Pemetrexed combined with cisplatin (or alternatively carboplatin), and vitamin supplementation, up to six cycles is recommended as a first-line systemic therapy option.	I, A
▪ Combination of bevacizumab with platinum pemetrexed is recommended as first-line systemic therapy option.	I, A
▪ Nivolumab plus ipilimumab, given up to 2 years equivalent dosing, is recommended as a first-line systemic therapy option regardless of histologies or PD-L1 status for unresectable MPM.	I, A
▪ Maintenance gemcitabine is not routinely recommended in patients with non-progressive MPM but may prolong PFS and can be considered when the benefits of deferring progression outweigh the inconveniences and toxicities of ongoing treatment.	II, C

▪ Maintenance pemetrexed is not recommended in patients with non-progressive MPM after first-line platinum-pemetrexed chemotherapy.	II, E
Systemic therapy for second line and beyond	
▪ Single-agent pembrolizumab in immunotherapy-naïve patients as second-line therapy has similar outcomes to single-agent chemotherapy and is a treatment option.	II, C
▪ Single-agent nivolumab is superior to BSC in pretreated immunotherapy-naïve patients and is a treatment option.	I, A
▪ Combination nivolumab-ipilimumab can be considered in immunotherapy-naïve patients as a second- or third-line treatment option.	II, C
▪ Reintroduction of platinum-pemetrexed [II, B] or pemetrexed chemotherapy [III, C] has second-line activity in selected circumstances, as suggested by ORRs.	III, C
▪ Single-agent gemcitabine or vinorelbine [II, B] has limited second-line activity, as suggested by ORRs or OS, with encouraging activity for gemcitabine-ramucirumab combination [III, C].	III, C
▪ There is no evidence basis for routine third-line therapy in MPM. Clinical trial participation should be considered.	V, C
Personalized therapy	
▪ PD-L1 expression, immune microenvironment analyses or tumor mutational burden should not be used to select patients for treatment with immune checkpoint inhibitors.	I, D
▪ No current treatment options warrant routine molecular testing of MPM.	III, D
▪ Screening of BAP1-deficient MPM patients for germline mutation is not recommended in the absence of family history suspicious for a BAP1 syndrome.	V, D
Role of Radiotherapy (RT)	
▪ RT can be considered for palliation of pain related to local infiltration of thoracic structures.	III, B
▪ The use of prophylactic RT of tracts after diagnostic or therapeutic pleural procedures to prevent chest wall metastases is not recommended.	I, D
▪ RT can be considered in an adjuvant setting after macroscopic complete resection to reduce the local failure rate; however, no evidence is available for its use as a standard treatment.	II, D

▪ When postoperative RT is applied, strict thoracic critical organs dose constraints must be adhered to in order to avoid toxicity to organs at risk.	II, A

A proposed treatment algorithm for multimodality management of MPM is shown in figure 1[20].

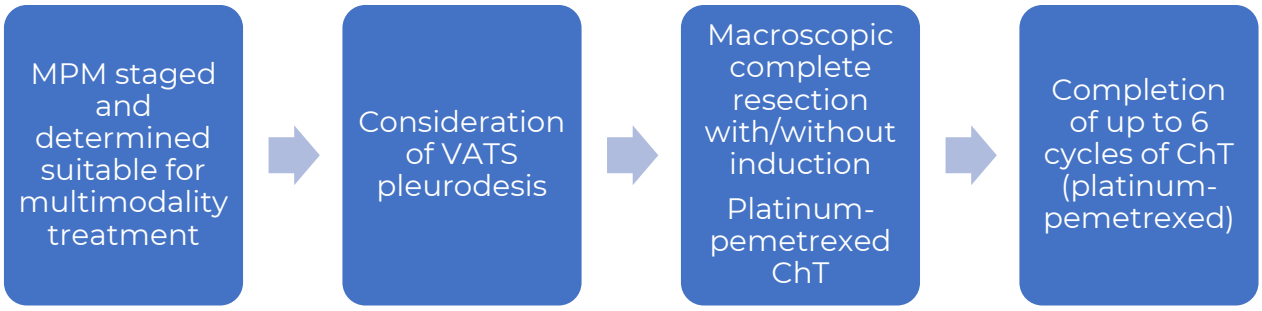

Figure 1. *Treatment algorithm for multimodality management of malignant pleural mesothelioma (ESMO guidelines)*

A proposed treatment algorithm for patients unsuitable for multimodality management (inoperable) of malignant pleural mesothelioma is shown in Figure 2.

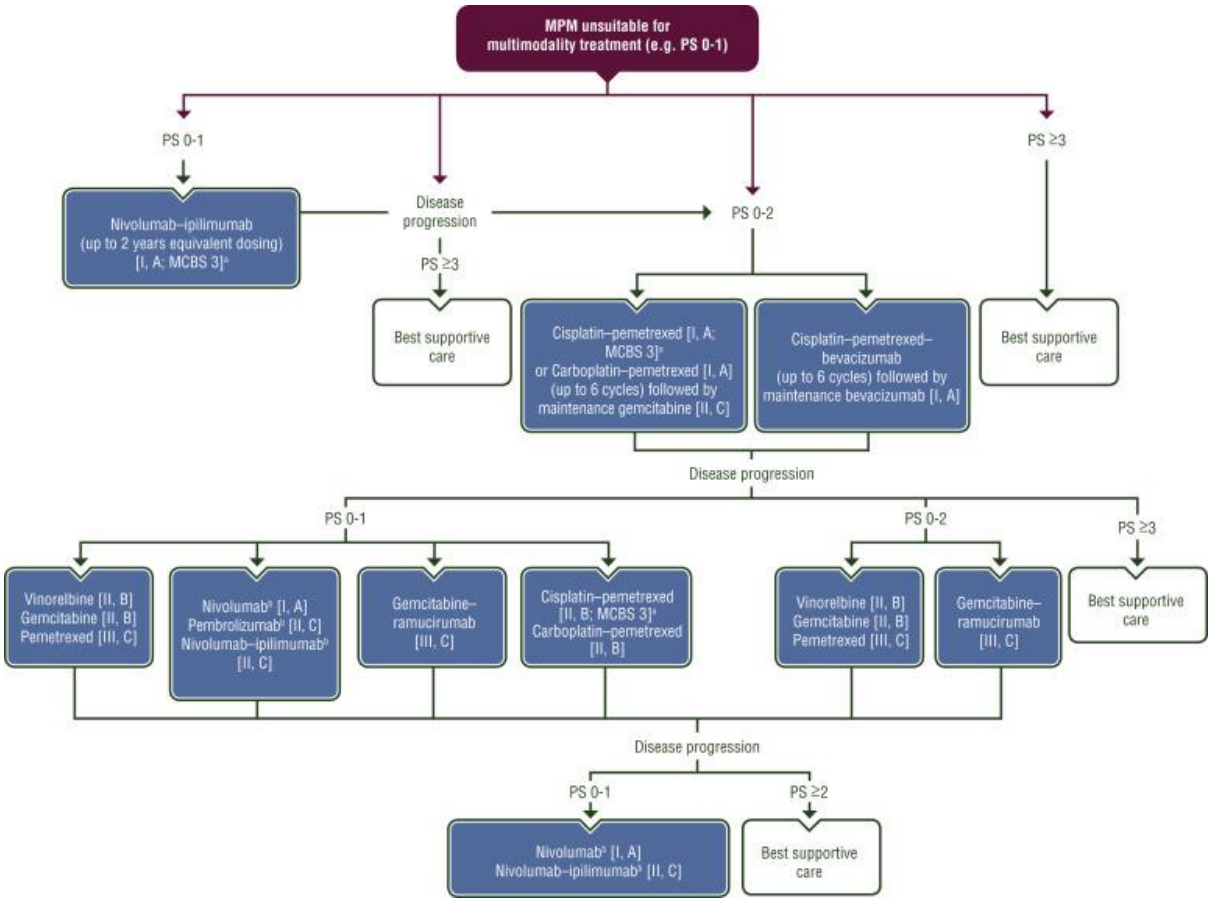

Figure 2. *Treatment algorithm for patients unsuitable for multimodality management (inoperable) of malignant pleural mesothelioma (retrieved from the 2021 ESMO guidelines)*

d. Follow-up, Long-Term Implications, and Survivorship

The follow-up, long-term implications, and survivorship recommendations for patients with malignant pleural mesothelioma according to the ESMO guidelines are shown in table 8.

Table 8. Follow-up, Long-Term Implications, and Survivorship Recommendations (ESMO Guidelines)

Recommendations	Strength
Follow-up, Long-Term Implications, and Survivorship	
▪ Early access to specialist palliative care at the time of diagnosis does not improve quality of life.	I, D
▪ Pleurodesis is useful in preventing recurrent effusions.	I, A
▪ For recurrent pleural effusions, an indwelling pleural catheter can provide good clinical benefit.	I, B
▪ For patients with indwelling pleural catheters aggressive draining is not superior in breathlessness control to symptomatic drainage.	I, E
▪ Response evaluation imaging is best carried out with contrast-enhanced CT scanning.	III, B

1.3.2 Peritoneal Surface Oncology Group International (PSOGI)/European Network for Rare Adult Solid Cancer (EURACAN) Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up of Peritoneal Mesothelioma (2020)

The Peritoneal Surface Oncology Group International (PSOGI)/European Network for Rare Adult Solid Cancer (EURACAN) released in 2020 clinical practice guidelines for diagnosis, treatment, and follow up of diffuse malignant peritoneal mesothelioma (DPeM)[21]. The key recommendations of the guideline are outlined in the following sections.

a. Incidence and Epidemiology

- Despite a very low level of evidence, individuals with any history of asbestos exposure currently or in the past could be advised to undergo a screening program, with an abdominal ultrasound every year, to improve early detection of DPeM (II,D)
- For the pathological diagnosis of PM, the analysis of adequate tissue specimens obtained from core needle biopsy or explorative laparoscopy is

mandatory, rather than a cytologic examination of serosal effusion or material collected by fine needle biopsy (I,A).

- The pathologic report must mention the histological subtype, the Ki-67 index and the nodal status (if appropriate). The mention of the sub-classification of epithelioid (tubulopapillary and solid/ deciduoid), the invasiveness, the mitotic rate, the nuclear grade, and the nuclear size are optional.
- Cross sectional imaging with CT for preoperative evaluation for DPeM should be the preferred diagnostic imaging modality (I,A).

b. Preoperative Workup

- MRI in the diagnostic and preoperative workup of PM patients could be one of the diagnostic imaging modality (II,B).
- PET/CT in the diagnostic and preoperative workup of peritoneal mesothelioma patients could be one of the diagnostic imaging modalities (II,C).
- The determination of baseline serum CA125 level could be included in the preoperative workup of DPEM patients (II,B).
- The determination of baseline serum mesothelin level could be included in the preoperative workup of DPeM patients (II,C).

c. Laparoscopy

- Laparoscopic evaluation in the preoperative workup of DPeM patients could be performed to better characterize the preoperative peritoneal cancer index and disease resectability (II,B).
- This preoperative laparoscopy should be done by a surgeon with expertise in PSM, with midline placement of trocars to allow excision in a subsequent operation for prevention of port site recurrence, with thorough evaluation of the peritoneal cavity with assessment of peritoneal cancer index (PCI), serosal and mesentery.

d. Treatment

- The selection for the best management strategy for DPeM patients by a **Multidisciplinary Team** involved or specialized in PSM is mandatory (I,A).
- In non-operable and/or non resectable DPeM patients (palliative patients), platinum-based systemic chemotherapy should be proposed rather than best supportive care. The best proposed regimen is the combination of cisplatin and pemetrexed, second choice cisplatin and gemcitabine (I,B).
- **Adjuvant combined systemic chemotherapy** should be proposed rather than direct follow-up, in DPeM patients treated with CRSHIPEC, and with at least one bad prognosis factor (CC-score > 1, sarcomatoid or biphasic subtype, lymph node involvement, Ki67 > 9%, PCI>17) (II,B).

- DPeM patients treated with CRS-HIPEC and with a favorable prognostic profile (complete cytoreduction and epithelioid subtype and no lymph node involvement and Ki67 9% and PCI 17) could be managed by follow-up alone. The benefit from adjuvant systemic chemotherapy is uncertain in these patients (II,B/C).
- **Locoregional adjuvant therapy** [early postoperative intraperitoneal chemotherapy (EPIC) and/or non-hyperthermic intraperitoneal chemotherapy (NIPEC)], in association with systemic chemotherapy, could be proposed in DPeM patients submitted to CRS-HIPEC, as long as postoperative clinical conditions are sufficient (II,C).
- **Bidirectional chemotherapy** could be proposed in DPeM patients with good general condition, no extra-peritoneal metastases and, after staging laparoscopy, unresectable disease or with borderline resectability (large extent of the disease potentially resectable, with multiple visceral resections at high risk for postoperative complications and impaired quality of life), rather than an induction systemic chemotherapy with conversion intent. The proposed regimen is **pemetrexed IP and cisplatin IV** (II,C).
- **CRS-HIPEC** is recommended in DPeM patients rather than palliative systemic chemotherapy, provided that the patient has a **sufficient clinical condition** for a major operation, has re**sectable disease**, and that the treatment is done in a specialized Peritoneal Surface Malignancies (PSM) center (I,B).
- Four factors are judged to constitute an absolute **contraindication** for CRS-HIPEC in DPeM patients: sarcomatoid histology, massive small bowel serosa involvement, concomitant pleural disease and/or a retroperitoneal and/or cardiophrenic lymph node involvement.
- Seven factors are judged to constitute a relative contra-indication for CRS-HIPEC in DMPM patients: - a biphasic histology, - a disease not amenable by cytoreduction down to CC-0/1, - a Ki-67 > 9% in the preoperative pathological report, - a PCI>17 in the pre-cytoreduction evaluation, - the combination of a high risk subset with Ki-67 > 9% and PCI>17 according to preoperative workup, - a massive small bowel mesentery involvement, - and/or a massive diaphragmatic involvement.
- A complete parietal peritonectomy during CRS for DPeM patients could be considered, as an option to selective parietal peritonectomy, regardless of PCI, in order to maximize locoregional disease control and eventually the long-term oncological outcomes (II,C).
- The dissection of suspicious retroperitoneal lymph nodes, and the sampling of non-suspicious nodes, could be considered during CRS, in order to enhance the prognostic characterization of the patient (II,C).

- **Platinum-based HIPEC** after a complete CRS down to residual disease 2.5 mm, could be considered in DPeM patients as an **option to systemic treatment** (II,B).
- **Cisplatin and Doxorubicin** is judged to be the **best drug regimen recommended for HIPEC** (I,C).

e. Follow-up

- A follow-up extended to **7 years after CRS-HIPEC** could be considered in DPeM patients (II,B).
- The follow-up during the first 2 years and onward after CRS-HIPEC is proposed to be performed every 6 months and to include: - a physical examination - a thoracic/abdominal/pelvic CT scan, - and a biomarker CA125 dosage (I,C).
- In recurrent DMPM patients with good general condition, resectable disease, and favorable prognostic profile (young age, epithelioid subtype, time to recurrence > 1 year, limited PCI), iterative CRS-HIPEC could be considered (II,B).

A proposed treatment algorithm for management of DPeM is shown in figure 3.

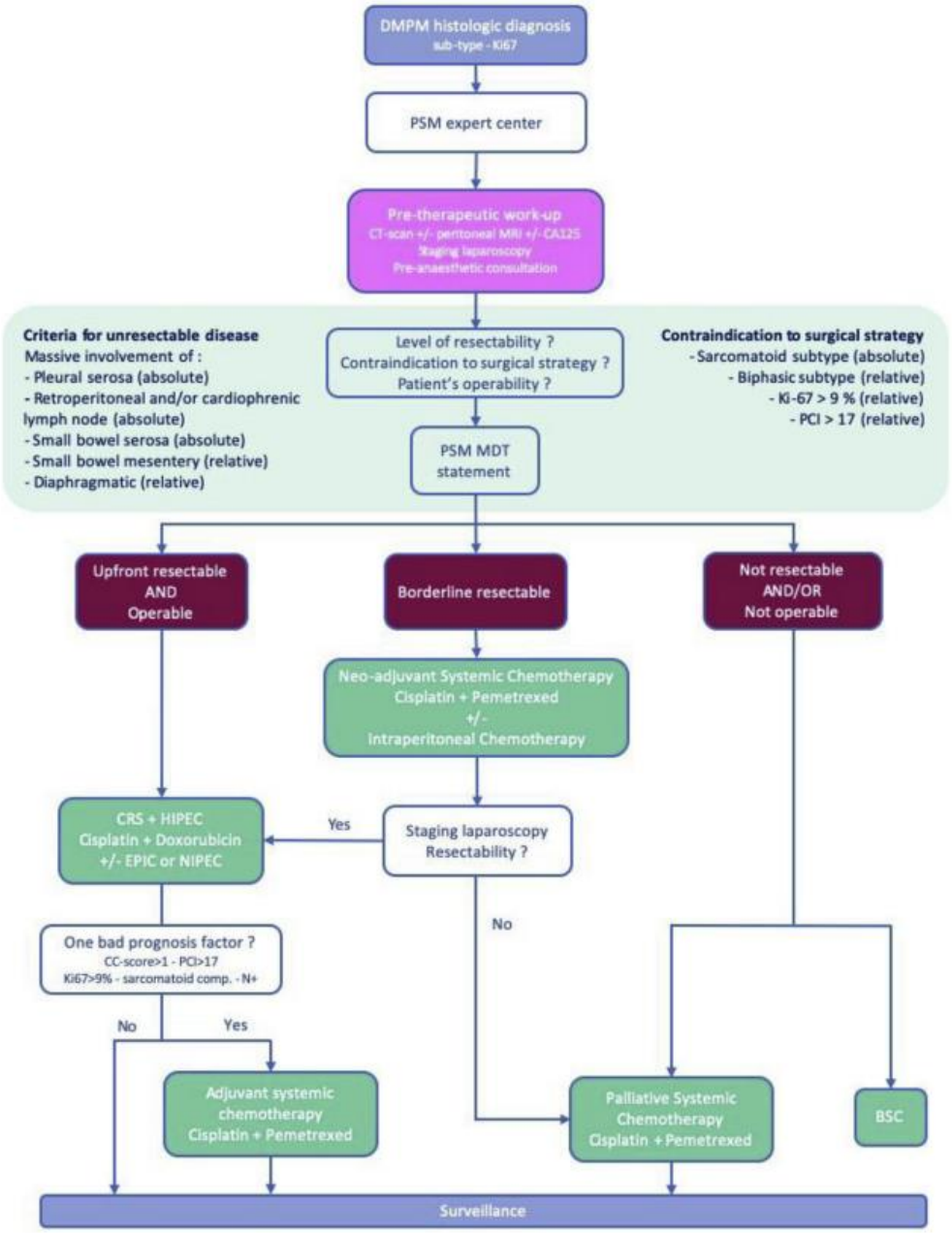

Figure 3. *Flowchart of DPeM management (retrieved from the 2020 PSOGI/EURACAN guidelines)*

1.3.3 European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS)/European Association for Cardio-Thoracic Surgery (EACTS)/European Society for Radiotherapy and Oncology (ESTRO) Guidelines for the Management of Malignant Pleural Mesothelioma (2020)

The European Respiratory Society (ERS), European Society of Thoracic Surgeons (ESTS), European Association for Cardio-Thoracic Surgery (EACTS), and the European Society for Radiotherapy and Oncology (ESTRO) released in 2020 guidelines for the management of malignant pleural mesothelioma[22]. The key recommendations of the guideline are outlined in the following sections.

a. 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-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 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 centers of excellence and as part of multimodality treatment. Patients with sarcomatoid or sarcomatoidpredominant 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).

b. 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 (moderate recommendation, low quality of evidence).
- Should radiotherapy be used to prevent procedure-tract metastases (drain site parietal seeding) in patients with MPM?
    - 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.

c. Medical treatment

- 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 bevacizumab be added to first line standard chemotherapy in patients with MPM?
    - 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 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.

d. 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 registered in a large institutional database.

e. 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.

1.4 International Guidelines

1.4.1 Society for Immunotherapy of Cancer (SITC) Clinical Practice Guideline on Immunotherapy for the Treatment of Lung Cancer and Mesothelioma (2022)

The Society for Immunotherapy of Cancer (SITC) released in 2022 clinical practice guidelines on immunotherapy for the treatment of lung cancer and mesothelioma[23]. The key treatment recommendations relevant for mesothelioma are outlined in the following sections:

a. First-line Treatment of Mesothelioma

- For the diagnosis of mesothelioma, an adequate tissue biopsy should be used. The pathology report for mesothelioma should preferably include the histologic subtype, specifically epithelioid, biphasic, or sarcomatoid.
- Germline genetic testing for BAP1 mutation should be considered for patients with mesothelioma especially those with a family history of mesothelioma or other BAP1 associated cancers such as uveal melanoma, cutaneous melanoma, kidney or bladder cancer, or age less than 60 years (LE:4).
- In newly diagnosed patients with mesothelioma, a multidisciplinary approach that includes consultation with thoracic surgeons, pulmonologists, radiation oncologists, and medical oncologists should be considered to determine if they are candidates for maximum cytoreductive operation such pleurectomy and decortication or extrapleural pneumonectomy with or without radiation therapy.
- Whenever possible, patients should be offered participation in clinical trials.
- For patients with epithelioid subtype mesothelioma, treatment with nivolumab plus ipilimumab may be considered based on comparable

outcomes to SOC chemotherapy. However, treatment decisions should be individualized and take into account the differing side effect profiles of combination immunotherapy and chemotherapy (LE:2).

- **For patients with non-epithelioid subtype mesothelioma, treatment with nivolumab plus ipilimumab is strongly recommended based on an almost twofold increase in median OS compared with stand of care chemotherapy** (LE:2).
- For patients with mesothelioma, routine PD-L1 testing is not recommended, as benefit from immunotherapy with nivolumab plus ipilimumab was seen regardless of PD-L1 expression (LE:2).
- Routine TMB testing is not recommended for patients with mesothelioma.
- For patients with mesothelioma that has progressed following front-line treatment with nivolumab and ipilimumab, platinum-based chemotherapy with pemetrexed should be considered (LE:2).
- Patients with mesothelioma that have progressed following immunotherapy and pemetrexed with platinum-based chemotherapy should be encouraged to enroll in clinical trials.

b. Radiographic Response to immunotherapy

- For patients commencing ICI-based therapy for lung cancer, a baseline CT should be performed within 4 weeks before the first dose of therapy.
- The first follow-up CT imaging on therapy should be performed 6–9 weeks (approximately 2–3 treatment cycles) after the commencement of ICI-based therapy, and the timing should be adapted to the dosing schedule of the systemic therapy.
- If a patient is clinically stable or improved, it is reasonable to continue therapy beyond radiographic progression. Repeat CT imaging should be performed within 4–8 weeks to rule out continued disease progression and monitor for toxicities.
- For a patient who has been treated with immunotherapy beyond radiographic progression and has continued disease progression at the time of follow-up imaging and/or clinical deterioration, strong consideration should be given to looking for an alternative systemic therapy.

c. Understudied Patients Populations

- For patients with advanced lung cancers and active autoimmune conditions or SOTs, the use of immunotherapy merits a thoughtful multidisciplinary approach requiring a discussion with the treating team, including subspecialists and the oncologist, and the patient regarding the risk of autoimmune activation against the potential for benefit with ICI treatment. Given the lack of prospective clinical trial data, whenever

possible patients in these groups should be encouraged to enroll in clinical trials.

- Baseline interstitial lung disease and/or a high risk for pneumonitis are relative contraindications to ICI therapy (LE:3).
- For patients with pre-existing autoimmune disorders that are controlled with chronic low dose immunosuppression, ICI therapy is not necessarily absolutely contraindicated. However, immunotherapy should be avoided in patients with poor control of autoimmune disease (requiring high doses of immunosuppressants) and in patients with life-threatening and/ or CNS autoimmune disease (LE:3).
- For patients with SOTs, the impact of graft rejection should be weighed against the potential benefit of ICI treatment. In most cases, the ramifications of graft rejection will outweigh the palliative benefits of ICI treatment, although renal transplant patients may represent an exception (LE:1).

1.5 Systematic Reviews/Meta-Analyses

A detailed search of PubMed and Cochrane databases for systematic reviews and meta-analysis on mesothelioma management didn't yield any result more recent than the detailed previous guidelines. This is probably due to the fact that the treatment guidelines for mesothelioma are constantly being updated with the many clinical trials and treatment alternatives emerging in the market.

1.6 Secondary and Tertiary Resources

The international guidelines detailed in previous sections being most updated, a detailed search of secondary and tertiary resources for additional guidelines, such as Google Scholar, the Ovid Health Technology Assessment Database, the National Institute for Health and Care Research Journals Library, and UpToDate did not yield any additional data that hasn't already been described.

Section 2.0 Drug Therapy

2.1 Alkylating agents

2.1.1 Carboplatin

Table 9. Carboplatin Drug Information

Scientific Name Carboplatin[26]	
Trade Name(s) on Saudi Market	Carboplatin (Ebewe, Hospira), Cartinum
SFDA Classification	Prescription
SFDA approved Indication	Yes, Carboplatin Ebewe, 2001; Cartinum, 2019; Carboplatin Hospira, 2020
FDA approved / off label	Yes, 1989
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2005
Indication (ICD-10)	C45
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating agent
SFDA Registration Number (New)	Carboplatin Ebewe: 2-355-01 (150mg); 3-355-01 (450mg) Carboplatin Hospira: 15-5287-20 (150mg); 16-5287-20 (450mg) Cartinum: 21-5223-19 (150mg); 22-5223-19 (450mg)
ATC Code	L01XA02
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	Target AUC 5 on day 1 every 3 weeks (in combination with pemetrexed) until disease progression, unacceptable toxicity, or for a maximum of 9 cycles
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult):

	Dose determination with Calvert formula uses GFR and, therefore, inherently adjusts for kidney dysfunction.
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used as a single agent or in combination with chemotherapy (pemetrexed); To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose (and/or dose per cycle) not to exceed a target AUC 6
ST (Step Therapy)	First-line treatment of pleural and peritoneal mesothelioma in combination with pemetrexed ± bevacizumab (preferred therapy for epitheliod histology) or with gemcitabine, in patients who are not candidates for cisplatin therapy. First-line treatment of peritoneal mesothelioma as part of HIPEC regimens. Second-line treatment of pleural and peritoneal mesothelioma in combination with pemetrexed ± bevacizumab (preferred if nivolumab/ipilimumab used in first-line), in patients who are not candidates for cisplatin therapy.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Maximum daily dose (and/or dose per cycle) not to exceed a target AUC 6
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Decreased serum Ca, K, Mg, gastrointestinal pain, nausea and vomiting, anemia, leukopenia, thrombocytopenia, increased liver enzymes, asthenia,

	pain, decreased creatinine clearance - Most serious: Ototoxicity, anemia, leukopenia, thrombocytopenia
Drug Interactions*	- Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Fexinidazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Topotecan, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Carboplatin is present in breast milk. Breastfeeding is not recommended.
Contraindications	History of severe allergic reaction to carboplatin, cisplatin, other platinum-containing formulations, or any component of the formulation; should not be used in patients with severe bone marrow depression or significant bleeding
Monitoring Requirements	CBC (with differential and platelet count), serum electrolytes, serum creatinine and BUN, CrCl, LFTs; audiology evaluations (children <6

	months of age); signs/symptoms of hypersensitivity reactions.
Precautions	- Bone marrow suppression - GI toxicity - Hepatic function abnormality - Hypersensitivity - Neurotoxicity - Ototoxicity - Renal toxicity - Vision loss
Black Box Warning	- Experienced physician - Bone marrow suppression - Vomiting - Hypersensitivity reactions
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for carboplatin in mesothelioma.

Conclusion Statement – Carboplatin

In mesothelioma (pleural/peritoneal), carboplatin is used in patients not candidates for cisplatin therapy in the first-line setting in combination with pemetrexed ± bevacizumab (preferred therapy for epitheliod histology) or in combination with gemcitabine. It is also used as second-line treatment of mesothelioma in combination with pemetrexed ± bevacizumab (preferred if nivolumab/ipilimumab used in first-line).

There is no data issued by HTA bodies regarding its use.

2.1.2 Cisplatin

Table 10. Cisplatin Drug Information

Scientific Name **Cisplatin[27]**	
Trade Name(s) on Saudi Market	Cisplatin (Ebewe, Hospira), Cipalin, Tinplat
SFDA Classification	Prescription
SFDA approved Indication	Yes, Cisplatin Ebewe, 2001; Cisplatin Jazeera Pharmaceutical Industries

	(JPI), 2018; Cisplatin Hospira, 2019; Tinplat, 2019
FDA approved / off label	Yes, 1978
EMEA approved / off label	Yes, 1996
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C45
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating agent
SFDA Registration Number (New)	Cisplatin Ebewe: 409222579 (10mg); 0409222580 (50mg) Cipalin: 288-334-18 (10mg); 289-334-18 (25mg); 290-334-18 (50mg) Cisplatin Hospira: 4-5287-19 (50mg) Tinplat: 29-5223-19 (10mg); 30-5223-19 (50mg)
ATC Code	L01XA01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	75 mg/m^2 on day 1 every 3 weeks (in combination with pemetrexed ± bevacizumab) 100 mg/m^2 on day 1 every 4 weeks or 80 mg/m^2 every 3 weeks (in combination with gemcitabine) *HIPEC Cisplatin+Doxorubicin regimen:* Cisplatin 50 mg/m^2 Doxorubicin 15 mg/m^2 (based on case-report data)[28]
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl ≥60 mL/mine: IV: No adjustment - CrCl 50 to <60 mL/min: IV: 75% of the dose - CrCl 40 to <50 mL/minute: IV: 50% of the dose

	- CrCl <40 mL/minute: Not recommended - Hemodialysis/PD: Poorly dialyzable due to rapid and high degree of protein binding: 50% of the dose after dialysis - CRRT/PIRRT: Use is not recommended - Nephrotoxicity during treatment: Patients that develop AKI (SCr >2 times baseline) may require discontinuation of therapy
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with other chemotherapy agents (pemetrexed ± bevacizumab or gemcitabine); To be used with antiemetics, hyperhydration
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Total dose per cycle not to exceed 120 mg/m^2
ST (Step Therapy)	First-line treatment of pleural and peritoneal mesothelioma in combination with pemetrexed ± bevacizumab (preferred therapy for epitheliod histology) or with gemcitabine. First-line treatment of peritoneal mesothelioma as part of HIPEC regimens. Second-line treatment of pleural and peritoneal mesothelioma in combination with pemetrexed ± bevacizumab (preferred if nivolumab/ipilimumab used in first-line)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Total dose per cycle not to exceed 120 mg/m^2
Maximum Daily Dose Pediatrics*	N/A

Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Neurotoxicity, nausea and vomiting, nephrotoxicity, anemia, leukopenia, thrombocytopenia, increased liver enzymes, ototoxicity - Most serious: Neurotoxicity, anemia, leukopenia, thrombocytopenia, hearing loss
Drug Interactions*	- Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Fexinidazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Topotecan, Vaccines (Inactivated/Non-Replicating)
Special Population	Renal Impairment
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Cisplatin is present in breast milk. Breastfeeding is not recommended.
Contraindications	Severe hypersensitivity to cisplatin or any component of the formulation
Monitoring Requirements	Blood counts, serum creatinine, BUN, CrCl, and serum electrolytes Neurological examination, consider audiometric and vestibular testing

	Monitor closely for signs/symptoms of infection, hypersensitivity reactions, neuropathy, ocular toxicity, tumor lysis syndrome, and secondary malignancies
Precautions	- Bone marrow suppression - Extravasation - GI toxicity - Hypersensitivity - Nephrotoxicity - Neurotoxicity - Ocular toxicity - Ototoxicity - Secondary malignancies - Tumor lysis syndrome
Black Box Warning	- Myelosuppression - Nausea and vomiting - Nephrotoxicity - Peripheral neuropathy
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for cisplatin in mesothelioma.

Conclusion Statement – Cisplatin

In mesothelioma (pleural/peritoneal), cisplatin is used in the first-line setting in combination with pemetrexed ± bevacizumab (preferred therapy for epitheliod histology) or in combination with gemcitabine. It is also used as second-line treatment of mesothelioma in combination with pemetrexed ± bevacizumab (preferred if nivolumab/ipilimumab used in first-line). It is also an agent used in HIPEC regimens for the management of selected cases of peritoneal mesothelioma (unicavitary PeM and epithelioid histology who are medically operable if a complete cytoreduction is achievable).

There is no data issued by HTA bodies regarding its use.

2.2 Antimetabolites

2.2.1 Gemcitabine

Table 11. Gemcitabine Drug Information

Scientific Name Gemcitabine[29]	
Trade Name(s) on Saudi Market	Gemcitabine Ebewe, Citabol, Gemcitabine Jazeera, Gemzar, Citarox, Gebtin, Gemcitabine Glenmark, Gemcitabine BOS
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2011
FDA approved / off label	Yes, 1998
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2006
Indication (ICD-10)	C45
Drug Class	Antineoplastic agent
Drug Sub-class	Antimetabolite (Pyrimidine Analog)
SFDA Registration Number (New)	Gemcitabine Ebewe: 48-355-11 (1g); 50-355-11 (200mg) Citabol: 3-796-15 (1g); 4-796-15 (200mg) Gemcitabine Jazeera: 0712222984 (200mg); 0712222985 (1g) Gemzar:1-5396-19 (200mg) Citarox: 1-5251-19 (200mg); 10-5251-20 (1g) Gebtin: 72-5286-20 (1g); 73-5286-20 (200mg) Gemcitabine Glenmark: 1-5438-20 (200mg); 2-5438-20 (1000mg) Gemcitabine BOS: 0301221548 (1g)
ATC Code	L01BC05
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for concentrate for solution for injection
Route of Administration	Intravenous

Dose (Adult) [DDD]*	1000 mg/m^2 days 1, 8, and 15 every 28 days (in combination with cisplatin) 1,250 mg/m^2 days 1 and 8 every 21 days (in combination with cisplatin) 1,250 mg/m^2 days 1, 8, and 15 every 28 days (as a single agent)
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl ≥30 mL/min: No adjustment necessary - CrCl <30 mL/min: No adjustment necessary. However, increased risk of hematologic toxicity - Hemodialysis/ PD/CRRT/ PIRRT: No dosage adjustment necessary Hepatic Impairment (Adult): - Transaminases elevated (with normal bilirubin or total bilirubin <1.6 mg/dL): No dosage adjustment necessary - Serum bilirubin >1.6 mg/dL: Use initial dose of 800 mg/m^2; may escalate if tolerated - Total bilirubin ≥1.6 mg/dL: May begin with 80% of the usual gemcitabine dose and increase the dose if tolerated
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with chemotherapy (cisplatin or ramucirumab) or as a single agent (second-line setting); To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum dose per day 1000 mg/m^2
ST (Step Therapy)	First-line treatment of pleural and peritoneal mesothelioma in combination with cisplatin (useful in certain circumstances)

	Second-line treatment of pleural and peritoneal mesothelioma as a single agent or in combination with ramucirumab
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	1000 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Edema, drowsiness, skin rash, alopecia, nausea and vomiting, diarrhea, stomatitis, proteinuria, hematuria, anemia, neutropenia, thrombocytopenia, hemorrhage, increased liver function tests, infection, increased blood urea nitrogen, dyspnea, flu-like symptoms, fever - Most serious: hemolytic-uremic syndrome
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults, radiation therapy recipients
Pregnancy	Pregnancy Category D: Not used in pregnancy

Lactation	It is not known if gemcitabine is present in breast milk. Breastfeeding is not recommended during treatment and for at least 1 week after the last gemcitabine dose.
Contraindications	Known hypersensitivity to gemcitabine or any component of the formulation
Monitoring Requirements	CBC with differential and platelet count; LFTs, renal function, electrolytes, Pulmonary function Monitor for signs/symptoms of capillary leak syndrome, hemolytic uremic syndrome, hepatotoxicity, hypersensitivity, posterior reversible encephalopathy syndrome, and pulmonary toxicity.
Precautions	- Bone marrow suppression - Capillary leak syndrome - Hemolytic uremic syndrome - Hepatotoxicity - Hypersensitivity - Posterior reversible encephalopathy syndrome - Pulmonary toxicity
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for gemcitabine in mesothelioma.

Conclusion Statement – Gemcitabine

In mesothelioma (pleural/peritoneal), gemcitabine is used in the first-line setting in combination with cisplatin useful in certain circumstances). It is also used as second-line treatment of mesothelioma as a single agent or in combination with ramucirumab.

There is no data issued by HTA bodies regarding its use.

2.2.2 Pemetrexed

Table 12. Pemetrexed Drug Information

Scientific Name Pemetrexed[30]	
Trade Name(s) on Saudi Market	Pemitra ; Pemetrexed SPC ; Pemitax ; Alimta ; Almetra ; Alix ; Pemetrexed EPC
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2017
FDA approved / off label	Yes
EMEA approved / off label	Yes
MHRA approved / off label	Yes
PMDA approved / off label	Yes
Indication (ICD-10)	C45
Drug Class	Antineoplastic agent
Drug Sub-class	Antimetabolite (Pyrimidine Analog)
SFDA Registration Number (New)	Pemitra : 2310222780 Pemetrexed SPC : 1907233889 Pemitax : 0410200179 Alimta : 14-5117-19 Almetra : 80-5286-20 Alix : 1612211484 Pemetrexed EPC : 2711222935 (500 mg); 2711222934 (100 mg)
ATC Code	QL01BA04
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for concentrate for solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	500 mg/m^2 on day 1 of each 21-day cycle (as a single agent or in combination with cisplatin)
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl ≥45 mL/minute: No dosage adjustment necessary. - CrCl <45 mL/minute: Use is not recommended by the manufacturer (an insufficient

	number of patients have been studied for dosage recommendations). - Kidney toxicity during treatment: Withhold pemetrexed until CrCl is ≥45 mL/minute.
Prescribing edits*	AGE, MD, ST, PE, CU, QL
AGE (Age Edit)	No used in the pediatric population
CU (Concurrent Use)	To be used with cisplatin ± bevacizumab or as a single agent; To be used with antiemetics; To be used with folic acid/vitamin B12 supplementation
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum dose per day 500 mg/m^2
ST (Step Therapy)	First-line treatment of pleural and peritoneal mesothelioma in combination with cisplatin ± bevacizumab (preferred therapy for epitheliod histology) or as a single agent Second-line treatment of pleural and peritoneal mesothelioma in combination with cisplatin ± bevacizumab or as a single agent (preferred if nivolumab/ipilimumab used in first-line)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	500 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Desquamation, skin rash Anorexia, diarrhea, nausea, stomatitis, vomiting; Anemia, neutropenia, fatigue, pharyngitis - Most serious: Febrile neutropenia, Pulmonary embolism
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cedazuridine,

	Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults, radiation therapy recipients
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if pemetrexed is present in breast milk. Breastfeeding is not recommended during treatment and for 1 week after the last pemetrexed dose.
Contraindications	Severe hypersensitivity to pemetrexed or any component of the formulation
Monitoring Requirements	- CBC with differential and platelets - Renal function tests, total bilirubin, ALT, AST (periodic) - Pregnancy status - Monitor for signs/symptoms of mucositis and diarrhea, pulmonary toxicity, dermatologic toxicity, and radiation recall
Precautions	- Bone marrow suppression - Cutaneous reactions - GI toxicity - Hypersensitivity - Nephrotoxicity - Pulmonary toxicity - Radiation recall

	- Renal impairment - Third space fluids - Ibuprofen may reduce the clearance of pemetrexed
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the Haute Autorité de Santé **(HAS)**, National Institute for Health and Care Excellence (**NICE**), and Canadian Agency for Drugs and Technologies in Health (**CADTH**) HTA review and recommendations of pemetrexed in mesothelioma treatment options.

Table 13. Pemetrexed HTA Recommendations

Medication	Agency	Date – HTA Recommendation
Pemetrexed	HAS[31]	04/2016: Recommends **continued inclusion on the list of reimbursable products** for hospital use. • **Substantial actual benefit** and **Moderate clinical added value** in **first-line treatment of unresectable malignant pleural mesothelioma**. • In one randomized single-blind phase III study conducted in 456 adults with malignant pleural mesothelioma who did not receive prior systemic chemotherapy, the **median overall survival** (primary endpoint) with the pemetrexed/cisplatin combination (PEM/CIS) (12.1 months) was sup**erior to treatment with cisplatin as a monotherapy** (CIS) (9.3 months); HR=0.77; 95% CI [0.61-0.96]; p=0.02.
	NICE[32]	01/2008: Pemetrexed is **recommended** as a treatment option for **malignant pleural mesothelioma** only in people who have a World Health Organization (WHO) performance status of 0 or 1, who are considered to have **advanced disease** and for whom **surgical resection is considered inappropriate**. • The results of the EMPHACIS trial suggest that **pemetrexed plus cisplatin** confers a **survival**

		benefit of approximately 3 months compared with **cisplatin alone**. • The combination treatment also appears to demonstrate **advantages** in terms of 1**-year survival, median time to progressive disease, tumor response rate and quality of life**. • Pemetrexed plus cisplatin appears to offer greater survival benefits than cisplatin alone in patients with **advanced disease**. • Severe to life-threatening or disabling adverse events were statistically significantly more frequent in patients receiving pemetrexed plus cisplatin than in those receiving cisplatin alone. • The economic analyses carried out by the manufacturer and the Assessment Group, both indicated an incre**mental cost per QALY gained of greater than £60,000** when pemetrexed plus cisplatin was compared with cisplatin alone in the fully supplemented population. • Pemetrexed plus cisplatin, when compared with cisplatin alone, appears to have **lower ICERs in patients with advanced disease and/or good performance status**.

Conclusion Statement – Pemetrexed

In mesothelioma (pleural/peritoneal), pemetrexed is used in the first-line setting in combination with cisplatin ± bevacizumab (preferred therapy for epitheliod histology) or as a single agent. It is also used as second-line treatment of mesothelioma in combination with cisplatin ± bevacizumab or as a single agent (preferred if nivolumab/ipilimumab used in first-line).

Pemetrexed has received positive reviews from HAS and NICE in the malignant pleural mesothelioma indication:

- **HAS recommends the reimbursement** of pemetrexed, citing a **substantial actual benefit** and **moderate clinical added value** in **first-line treatment of unresectable malignant pleural mesothelioma**.
- **NICE** on the other hand **recommends pemetrexed** as a treatment option for **malignant pleural mesothelioma** only in people who have a World Health Organization (WHO) performance status of 0 or 1, who are considered to have **advanced disease** and for whom **surgical resection is**

considered inappropriate. The results of the EMPHACIS trial suggest that **pemetrexed plus cisplatin** confers a **survival benefit of approximately 3 months** compared with **cisplatin alone**, in addition to **advantages** in terms of 1**-year survival, median time to progressive disease, tumor response rate and quality of life.** The economic analyses indicate an incre**mental cost per QALY gained of greater than £60,000** when pemetrexed plus cisplatin was compared with cisplatin alone in the fully supplemented population. Pemetrexed plus cisplatin, when compared with cisplatin alone, appears to have **lower ICERs in patients with advanced disease and/or good performance status**.

2.3 Antimicrotubular Agents

2.3.1 Vinorelbine

Table 14. Vinorelbine Drug Information

Scientific Name **Vinorelbine**[33]	
Trade Name(s) on Saudi Market	Navelbine
SFDA Classification	Prescription
SFDA approved Indication	Yes, 1996
FDA approved / off label	Yes, 1962
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C45
Drug Class	Antineoplastic agent
Drug Sub-class	Antimicrotubular, Vinca Alkaloid
SFDA Registration Number (New)	1-5798-23 (10mg); 2-5798-23 (50mg)
ATC Code	L01CA04
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	30 mg/m^2 (maximum dose: 60 mg) once weekly for 6 doses (each cycle consists of 6 once-weekly doses), continue until disease progression
Dose (Pediatrics)	N/A
Adjustment	Hepatic Impairment (Adult):

	- Serum bilirubin ≤2 mg/dL: Administer 100% of dose. - Serum bilirubin 2.1 to 3 mg/dL: Administer 50% of dose - Serum bilirubin >3 mg/dL: Administer 25% of dose
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used with anti-emetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	60 mg
ST (Step Therapy)	First and second-line treatment of pleural and peritoneal mesothelioma as a single agent (useful in certain circumstances)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	60 mg
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Neurotoxicity, peripheral neuropathy, Alopecia, Nausea, vomiting, constipation, diarrhea, Neutropenia, leukopenia, anemia, Increased serum aspartate aminotransferase, Injection site reaction pain at injection site, Asthenia, Increased serum creatinine - Most serious: intestinal necrosis, intestinal obstruction, intestinal perforation, paralytic ileus, bone marrow depression, hepatotoxicity, neurotoxicity, febrile neutropenia, sepsis, pulmonary toxicity
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Nadofaragene

	Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if vinorelbine is present in breast milk. The manufacturer does not recommend breastfeeding during treatment and for 9 days after the final vinorelbine dose.
Contraindications	N/A
Monitoring Requirements	- CBC with differential and platelet count (prior to each dose, and after treatment), hepatic function tests. - Pregnancy status. - Monitor for new-onset pulmonary symptoms, for neuropathy, for signs/symptoms of constipation/ileus. - Monitor infusion site.
Precautions	- Bone marrow suppression - Extravasation - Gastrointestinal toxicity - Hepatotoxicity - Neuropathy - Pulmonary toxicity
Black Box Warning	- Bone marrow suppression
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield to any guidance for vinorelbine in mesothelioma.

Conclusion Statement – Vinorelbine

In mesothelioma (pleural/peritoneal), vinorelbine is used in the first-and second-line setting as a single agent.

There is no data issued by HTA bodies regarding its use.

2.4 Immune Checkpoint Inhibitors (ICIs)

2.4.1 Atezolizumab

Table 15. Atezolizumab Drug Information

Scientific Name Atezolizumab[34]	
Trade Name(s) on Saudi Market	Tecentriq
SFDA Classification	Prescription
SFDA Approved Indication	Yes; used off-label in peritoneal mesothelioma
FDA approved/off label	Yes; used off-label in peritoneal mesothelioma
EMEA approved/off label	Yes; used off-label in peritoneal mesothelioma
MHRA approved/off label	Yes; used off-label in peritoneal mesothelioma
PMDA approved/off label	Yes; used off-label in peritoneal mesothelioma
Indication (ICD-10)	C45. 1
Drug Class	Antineoplastic agent, monoclonal antibody
Drug Sub-Class	Immune Checkpoint Inhibitor (PDL-1 Inhibitor)
SFDA Registration Number (New)	285-24-17
ATC Code	L01XC32
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	1200 mg every 3 weeks

Adjustment	Renal impairment prior to treatment: No dosage adjustment Renal impairment during treatment: • Grade 2/3: withhold and resume after resolution to grade 0/1 • Grade 4: permanently discontinue Hepatic impairment prior to treatment: No dosage adjustment Hepatic impairment during treatment: If no tumor involvement of the liver: • AST/ALT increase to 3 up to 8 times ULN or total bilirubin increase by 1.5 up to 3 times ULN: withhold • AST/ALT increase to more than 8 times ULN or total bilirubin increase by more than 3 times ULN: permanently discontinue If tumor involvement of the liver: • Baseline AST/ALT 1 up to 3 times ULN and increase to 5 up to 10 times ULN, or baseline AST/ALT 3 up to 5 times ULN and increase to 8 up to 10 times ULN: withhold and resume after resolution to grade 0/1 • AST/ALT increase to more than 10 times ULN or total bilirubin increase to more than 3 times ULN: permanently discontinue Immune-mediated adverse reactions: • Withhold atezolizumab for grade 3 immune-mediated adverse reactions, and resume after resolution to grade 0/1 • Permanently for grade 4 or recurrent grade 3 adverse reactions
Dosage Form	Solution for injection
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with bevacizumab
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A

QL (Quantity Limit)	Maximum daily dose 1200 mg
ST (Step Therapy)	Second-line treatment of **peritoneal** mesothelioma in combination with bevacizumab (other recommended options).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	1200 mg
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: increased ALTs, increased alkaline phosphatase, thrombocytopenia, leukopenia, anemia, hyperkalemia, hyponatremia, hypocalcemia - Most serious: immune-mediated adverse reactions
Drug Interactions*	- Acetaminophen, antibiotics, corticosteroids, inhibitors of the proton pump: may diminish the therapeutic effect of anti-PD-L1 (risk C) - Ketoconazole: hepatotoxic effect enhanced by anti-PD-L1 (risk C) - Desmopressin: hyponatremic effect enhanced by anti-PD-L1 (risk C)
Special Population	N/A
Pregnancy	There is no data on the use of atezolizumab in pregnancy. Based on the mechanism of action, it can cause fetal harm when administered to pregnant women.
Lactation	The potential for absorption and harm to the infant is unknown. It is advised not to breastfeed during treatment and for at least 5 months after the last dose.
Contraindications	Known hypersensitivity to the product or its components
Monitoring Requirements	At baseline and periodically during treatment: - LFTs (AST/ALT/bilirubin) - Serum creatinine

	- Thyroid function - Serum glucose - CBC with differential Pregnancy status Signs and symptoms of immune-mediated adverse reactions HBV screening prior to initiation (do not delay treatment for screening results)
Precautions	- Immune-mediated adverse reactions - Cardiovascular toxicity - Dermatologic toxicity - Endocrinopathies (adrenal insufficiency, diabetes mellitus, thyroid disorders) - Gastrointestinal adverse effects - Hepatotoxicity - Nephrotoxicity - Infusion-related reactions - Ocular toxicity - Pulmonary toxicity
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for atezolizumab in mesothelioma.

Conclusion Statement – Atezolizumab

In mesothelioma, atezolizumab is used in the second-line setting of **peritoneal** mesothelioma in combination with bevacizumab.

There is no data issued by HTA bodies regarding its use.

2.4.2 Ipilimumab

Table 16. Ipilimumab Drug Information

Scientific Name Ipilimumab[35]	
Trade Name(s) on Saudi Market	Yervoy
SFDA Classification	Prescription
SFDA approved Indication	Yes
FDA approved / off label	Yes
EMEA approved / off label	Yes
MHRA approved / off label	Yes
PMDA approved / off label	Yes
Indication (ICD-10)	C45
Drug Class	Antineoplastic agent, monoclonal antibody
Drug Sub-class	Immune Checkpoint Inhibitor (CTLA4 Inhibitor)
SFDA Registration Number (New)	22-21-15
ATC Code	L01XC11
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Malignant pleural mesothelioma, unresectable; first-line therapy:** 1 mg/kg once every 6 weeks (in combination with nivolumab) until disease progression, unacceptable toxicity, or for up to 2 years in patients without disease progression
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): *Kidney impairment **prior** to treatment initiation:* No adjustment necessary *Kidney toxicity **during** treatment:* *Immune-mediated nephritis with kidney dysfunction:* - Grade 2 or grade 3 serum creatinine elevation: Withhold ipilimumab; resume ipilimumab after complete or partial (to grade 0 or 1) resolution after corticosteroid taper. Permanently

	discontinue if no complete or partial response within 12 weeks of last ipilimumab dose. - Grade 4 serum creatinine elevation: Permanently discontinue ipilimumab. Hepatic Impairment (Adult): *Hepatic impairment **prior** to treatment initiation:* No adjustment necessary. Has not been studied in severe hepatic impairment. *Hepatic impairment **during** treatment initiation* ● Immune-mediated hepatitis without tumor involvement of the liver: - AST or ALT >3 to ≤8 × ULN or total bilirubin >1.5 to ≤3 × ULN: Withhold ipilimumab. Resume with complete or partial resolution (to grade 0 or 1) of hepatitis after corticosteroid taper. - AST or ALT >8 × ULN or total bilirubin >3 × ULN: Discontinue permanently. ● Immune-mediated hepatitis with tumor involvement of the liver: - If baseline AST or ALT >1 to ≤3 × ULN and increases to >5 to ≤10 × ULN or baseline AST or ALT >3 to ≤5 × ULN and increases to >8 to ≤10 × ULN: Withhold ipilimumab. Resume with complete or partial resolution of hepatitis after corticosteroid taper. - AST or ALT increases to >10 × ULN or total bilirubin increases to >3 × ULN: Discontinue ipilimumab permanently.
Prescribing edits*	MD, CU, ST, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used with nivolumab
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 3 mg/Kg
ST (Step Therapy)	First-line treatment of pleural and peritoneal mesothelioma in combination

	with nivolumab (preferred therapy for biphasic or sarcomatoid histology) Second-line treatment of pleural and peritoneal mesothelioma in combination with nivolumab (preferred if chemotherapy used in first-line).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	3 mg/Kg
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Pruritus, skin rash, hypocalcemia, hyperglycemia, hypokalemia, hyponatremia, weight loss, colitis, decreased appetite, diarrhea, increased serum amylase, increased serum lipase, nausea, vomiting, anemia, lymphocytopenia, hepatitis, fatigue, arthralgia, musculoskeletal pain, increased serum creatinine, cough, dyspnea, fever. - Most serious: Arteritis (temporal), myocarditis, pericarditis, thyroiditis, aplastic anemia, systemic inflammatory response syndrome, demyelinating disease, encephalitis, Guillain-Barre syndrome, meningitis, polymyalgia rheumatica, polymyositis, rhabdomyolysis,
Drug Interactions*	- Risk D: Corticosteroids (May diminish the therapeutic effect of ICIs); Vemurafenib - Risk C: Acetaminophen, Antibiotics, Inhibitors of the Proton Pump, (May diminish the therapeutic effect of ICIs); Ketoconazole (Enhanced hepatotoxic effect).
Special Population	Older adults
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if ipilimumab is present in breast milk. The manufacturer recommends discontinuing breastfeeding

	during treatment and for 3 months after the last ipilimumab dose.
Contraindications	N/A
Monitoring Requirements	- PD-L1 expression - Hepatic (ALT, AST, and total bilirubin) and kidney function (serum creatinine), thyroid function, blood glucose - Pregnancy status - Monitor closely for signs/symptoms of immune-mediated adverse reactions, including adrenal insufficiency, hypophysitis, thyroid disorders, diabetes mellitus, diarrhea/colitis, pneumonitis, rash/dermatologic toxicity, ocular disorders, encephalitis - Monitor for signs/symptoms of infusion-related reactions
Precautions	- Adverse reactions (immune mediated) - Dermatologic toxicities - Endocrinopathies - GI toxicity - Hepatotoxicity - Infusion-related reactions - Nephrotoxicity - Ocular toxicity - Pulmonary toxicity - Hematopoietic stem cell transplant - Multiple myeloma
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the Haute Autorité de Santé **(HAS)**, National Institute for Health and Care Excellence (**NICE**), Canadian Agency for Drugs and Technologies in Health (**CADTH**), and the Institute for Quality and Efficiency in Health Care (**IQWIG**) HTA review and recommendations of the combination of nivolumab + ipilimumab in mesothelioma treatment options.

Table 17. Nivolumab + Ipilimumab HTA Recommendations

Medication	Agency	Date – HTA Recommendation
Nivolumab + Ipilimumab	HAS[36]	11/2021: **Favorable opinion for reimbursement in the first-line treatment of adult patients with unresectable malignant pleural mesothelioma**. • **Therapeutic improvement** compared to pemetrexed and platinum-based chemotherapy. • The Committee considers that **the clinical benefit** of the **nivolumab/ipilimumab combination** is **substantial** in the MA indication. • The Transparency Committee considers that the nivolumab/ipilimumab combination provides a **minor clinical added value (CAV IV) compared to pemetrexed and platinum-based chemotherapy** in the **first-line treatment** of adult patients with **unresectable malignant pleural mesothelioma**. Considering: • Demonstration of the **superiority** of the **nivolumab + ipilimumab** combination compared to **chemotherapy alone** (pemetrexed + platinum), in terms of **overall survival**, with an individual estimate of an absolute improvement of 4 months, HR = 0.74 [CI96.6%: 0.60-0.91], deemed to be clinically relevant in a randomized, open-label phase 3 study. Despite that: • the **time to observation of an improvement in overall survival** of more than **5 months** (crossing over of survival curves at 5 months) • the difficulty in differentiating between the proportion attributable (efficacy and toxicity) to each immunotherapy (nivolumab/ipilimumab), and hence the specific value of the combination of these two drugs compared to monotherapy (nivolumab or ipilimumab) related to the design of the CHECKMATE 743 study;

		• the **toxicity profile of nivolumab + ipilimumab**, marked by he development of an immunological AE, and infusion-related reactions.
Nivolumab + Ipilimumab	NICE[37]	08/2022: Nivolumab plus ipilimumab is **recommended** as an option for **untreated unresectable malignant pleural mesothelioma** in adults with performance status 0-1. • Standard care for untreated unresectable malignant pleural mesothelioma is chemotherapy. • The clinical trial evidence was in people with an ECOG performance status of 0 or 1. **Nivolumab plus ipilimumab improves overall survival compared with chemotherapy**, but its long-term treatment effect is uncertain (CheckMate 743 trial). • Nivolumab plus ipilimumab might **improve progression-free survival** but the evidence is uncertain. • PD-L1 status is not tested routinely in the NHS, so is not considered in decision making. • Nivolumab plus ipilimumab may improve quality of life. • The safety profile of nivolumab plus ipilimumab is acceptable. • A 2-year stopping rule for nivolumab plus ipilimumab and a 6-cycle stopping rule for chemotherapy is appropriate. • Nivolumab plus ipilimumab likely **meets NICE's criteria for being a life-extending treatment at the end of life**. • Taking this into account, the **cost-effectiveness estimates** for nivolumab plus ipilimumab were **within the range that NICE normally considers an acceptable use of NHS resources**. So, it is recommended.
Nivolumab + Ipilimumab	CADTH[38]	08/2021: CADTH recommends that **nivolumab plus ipilimumab should be reimbursed** by public drug plans for the treatment of **malignant pleural mesothelioma** to treat patients who have **not received prior systemic treatment** for MPM

		and who have good performance status at the start of treatment. • Evidence from a clinical trial demonstrated that nivolumab plus ipilimumab **improved overall survival** in adults with unresectable MPM with good performance status and who had not received prior MPM treatment. • Based on public list prices, nivolumab plus ipilimumab **is not considered cost-effective** at a willingness to pay of $50,000 per quality-adjusted life-year (QALY) for the indicated population relative to currently reimbursed alternatives. • Economic evidence suggests that **a price reduction of at least 72% is needed** for both nivolumab and ipilimumab to ensure this combination is cost-effective at a $50,000 per QALY threshold. • Based on public list prices, **the 3-year budget impact of nivolumab plus ipilimumab is $72 million**.
Nivolumab + Ipilimumab	IQWIG[39]	08/2021: **First-line treatment** of **unresectable malignant pleural mesothelioma** in adults. • Patients with **epithelioid** tumor histology: **added benefit not proven**. • Patients with **non-epithelioid** tumor histology: **indication of considerable added benefit**.

Conclusion Statement – Ipilimumab

In mesothelioma (pleural/peritoneal), ipilimumab is used in the first-line setting in combination with nivolumab (preferred therapy for (preferred therapy for biphasic or sarcomatoid histology). It is also used as second-line treatment of mesothelioma in combination with nivolumab (preferred if chemotherapy used in first-line).

The Nivolumab plus Ipilimumab immunotherapy combination has received positive reviews from HAS, NICE, CADTH, and IQWIG in the malignant pleural mesothelioma indication:

- **HAS recommends the reimbursement** of nivolumab + ipilimumab in the **first-line treatment of adult patients with unresectable malignant pleural mesothelioma**, citing a **therapeutic improvement** compared to

pemetrexed and platinum-based chemotherapy, a **substantial clinical benefit**, and a **minor clinical added value (CAV IV)**

- **NICE** guidance **recommends** nivolumab + ipilimimab as an option for **untreated unresectable malignant pleural mesothelioma** in adults with performance status 0-1, citing **improved overall survival and progression free survival compared with chemotherapy**, and **meeting NICE's criteria for being a life-extending treatment at the end of life**. The **cost-effectiveness estimates** for nivolumab plus ipilimumab were **within the range that NICE normally considers an acceptable use of NHS resources**.
- CADTH recommends that **nivolumab plus ipilimumab should be reimbursed** by public drug plans for the treatment of **malignant pleural mesothelioma** to treat patients who have **not received prior systemic treatment** for MPM and who have good performance status. The committee cites that nivolumab plus ipilimumab **improved overall survival** in adults with unresectable MPM with good performance status and who had not received prior MPM treatment. However, nivolumab plus ipilimumab **is not considered cost-effective** at a willingness to pay of $50,000 per QALY for the indicated population relative to currently reimbursed alternatives. **A price reduction of at least 72% is needed** for both nivolumab and ipilimumab to ensure this combination is cost-effective at a $50,000 per QALY threshold.
- For **IQWIG**, the added benefit of the combination nivolumab + ipilimumab depends on the **tumor histology**. In patients with **epithelioid** tumor histology the **added benefit of the combination is not proven**, while in patients with **non-epithelioid** tumor histology there's an **indication of considerable added benefit**. This aligns with the NCCN preferred treatment recommendations stated for each histological subtype.

2.4.3 Nivolumab

Table 18. Nivolumab Drug Information

Scientific Name Nivolumab[40]	
Trade Name(s) on Saudi Market	Opdivo
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2015 (used off-label)
FDA approved / off label	Yes, 2014
EMEA approved / off label	Yes, 2015
MHRA approved / off label	Yes, date not available
PMDA approved / off label	Yes, 2015
Indication (ICD-10)	C45

Drug Class	Antineoplastic agent, monoclonal antibody
Drug Sub-class	Immune Checkpoint Inhibitor (PD-1 Inhibitor)
SFDA Registration Number (New)	2-960-15 (40 mg); 3-960-15 (100 mg)
ATC Code	L01XC17
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Malignant pleural mesothelioma, unresectable:** 360 **mg** once every 3 weeks (in combination with ipilimumab); continue until disease progression, unacceptable toxicity, or for up to 2 years in patients without disease progression.
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): *Kidney impairment **prior** to treatment initiation:* No adjustment necessary *Kidney toxicity **during** treatment:* *Immune-mediated nephritis with kidney dysfunction:* - Grade 2 or grade 3 serum creatinine elevation: Withhold nivolumab; resume nivolumab after complete or partial (to grade 0 or 1) resolution after corticosteroid taper. Permanently discontinue if no complete or partial response within 12 weeks of last nivolumab dose. - Grade 4 serum creatinine elevation: Permanently discontinue nivolumab. Hepatic Impairment (Adult): *Hepatic impairment **prior** to treatment initiation:* No adjustment necessary. Has not been studied in severe hepatic impairment. *Hepatic impairment **during** treatment initiation* ● Immune-mediated hepatitis without tumor involvement of the liver:

	- AST or ALT >3 to ≤8 × ULN or total bilirubin >1.5 to ≤3 × ULN: Withhold nivolumab. Resume with complete or partial resolution (to grade 0 or 1) of hepatitis after corticosteroid taper. - AST or ALT >8 × ULN or total bilirubin >3 × ULN: Discontinue permanently. ● Immune-mediated hepatitis with tumor involvement of the liver: - If baseline AST or ALT >1 to ≤3 × ULN and increases to >5 to ≤10 × ULN or baseline AST or ALT >3 to ≤5 × ULN and increases to >8 to ≤10 × ULN: Withhold nivolumab. Resume with complete or partial resolution of hepatitis after corticosteroid taper. - AST or ALT increases to >10 × ULN or total bilirubin increases to >3 × ULN: Discontinue nivolumab permanently.
Prescribing edits*	MD, CU, ST, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used with ipilimumab
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 480 mg
ST (Step Therapy)	First-line treatment of pleural and peritoneal mesothelioma in combination with ipilimumab (preferred therapy for biphasic or sarcomatoid histology) Second-line treatment of pleural and peritoneal mesothelioma in combination with ipilimumab (preferred if chemotherapy used in first-line).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	480 mg
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Edema, hypertension, pruritus, skin rash, vitiligo, hypercalcemia, hyperglycemia,

	hyperkalemia, hyperthyroidism, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypothyroidism, increased serum albumin, weight loss, abdominal pain, decreased appetite, diarrhea, increased serum amylase, increased serum lipase, nausea, vomiting, anemia, leukopenia, , neutropenia, hepatitis, antibody development, dizziness, headache, arthralgia, asthenia, increased serum creatinine, cough, dyspnea, fever. - Most serious: Acute coronary syndrome, vasculitis, immune-mediated myocarditis, pericarditis, Stevens-Johnson syndrome, toxic epidermal necrolysis, hypothyroidism, hyperthyroidism, adrenocortical insufficiency, hypophysitis, type 1 diabetes mellitus, Immune-mediated colitis, immune thrombocytopenia, autoimmune hemolytic anemia, acquired blood coagulation disorder (hemophilia), disseminated intravascular coagulation, immune-mediated hepatitis and nephritis, uveitis, cerebral hemorrhage, myasthenia gravis, reversible posterior leukoencephalopathy syndrome, pneumonitis
Drug Interactions*	- Risk D: Corticosteroids (May diminish the therapeutic effect of ICIs) - Risk C: Acetaminophen, Antibiotics, Efgartigimod, Inhibitors of the Proton Pump, Rozanolixizumab (May diminish the therapeutic effect of ICIs); Desmopressin (Enhanced hyponatremia); Ketoconazole (Enhanced hepatotoxic effect).
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy

Lactation	It is not known if nivolumab is present in breast milk. The manufacturer recommends discontinuing breastfeeding during treatment and for 5 months after the last nivolumab dose.
Contraindications	N/A
Monitoring Requirements	- PD-L1 expression - Hepatic (ALT, AST, and total bilirubin) and kidney function (serum creatinine), thyroid function, blood glucose - Pregnancy status - Monitor closely for signs/symptoms of immune-mediated adverse reactions, including adrenal insufficiency, hypophysitis, thyroid disorders, diabetes mellitus, diarrhea/colitis, pneumonitis, rash/dermatologic toxicity, ocular disorders, encephalitis - Monitor for signs/symptoms of infusion-related reactions
Precautions	- Adverse reactions (immune mediated) - Infusion-related reactions - Auto-immune disorders - Hematopoietic stem cell transplant - Multiple myeloma - Myasthenia gravis
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the Haute Autorité de Santé **(HAS)**, National Institute for Health and Care Excellence (**NICE**), Canadian Agency for Drugs and Technologies in Health (**CADTH**), and the Institute for Quality and Efficiency in Health Care (**IQWIG**) HTA review and recommendations of the combination nivolumab + ipilimumab in mesothelioma treatment options.

Table 19. Nivolumab + Ipilimumab HTA Recommendations

Medication	Agency	Date – HTA Recommendation
Nivolumab + Ipilimumab	HAS[36]	11/2021: **Favorable opinion for reimbursement in the first-line treatment of adult patients with unresectable malignant pleural mesothelioma**.

		• **Therapeutic improvement** compared to pemetrexed and platinum-based chemotherapy. • The Committee considers that **the clinical benefit** of the **nivolumab/ipilimumab combination** is **substantial** in the MA indication. • The Transparency Committee considers that the nivolumab/ipilimumab combination provides a **minor clinical added value (CAV IV) compared to pemetrexed and platinum-based chemotherapy** in the **first-line treatment** of adult patients with **unresectable malignant pleural mesothelioma**. Considering: • Demonstration of the **superiority** of the **nivolumab + ipilimumab** combination compared to **chemotherapy alone** (pemetrexed + platinum), in terms of **overall survival**, with an individual estimate of an absolute improvement of 4 months, HR = 0.74 [CI96.6%: 0.60-0.91], deemed to be clinically relevant in a randomized, open-label phase 3 study. Despite that: • the **time to observation of an improvement in overall survival** of more than **5 months** (crossing over of survival curves at 5 months) • the difficulty in differentiating between the proportion attributable (efficacy and toxicity) to each immunotherapy (nivolumab/ipilimumab), and hence the specific value of the combination of these two drugs compared to monotherapy (nivolumab or ipilimumab) related to the design of the CHECKMATE 743 study; • the **toxicity profile of nivolumab + ipilimumab**, marked by he development of an immunological AE, and infusion-related reactions.
Nivolumab + Ipilimumab	NICE[37]	08/2022: Nivolumab plus ipilimumab is **recommended** as an option for **untreated**

		unresectable malignant pleural mesothelioma in adults with performance status 0-1. • Standard care for untreated unresectable malignant pleural mesothelioma is chemotherapy. • The clinical trial evidence was in people with an ECOG performance status of 0 or 1. **Nivolumab plus ipilimumab improves overall survival compared with chemotherapy**, but its long-term treatment effect is uncertain (CheckMate 743 trial). • Nivolumab plus ipilimumab might **improve progression-free survival** but the evidence is uncertain. • PD-L1 status is not tested routinely in the NHS, so is not considered in decision making. • Nivolumab plus ipilimumab may improve quality of life. • The safety profile of nivolumab plus ipilimumab is acceptable. • A 2-year stopping rule for nivolumab plus ipilimumab and a 6-cycle stopping rule for chemotherapy is appropriate. • Nivolumab plus ipilimumab likely **meets NICE's criteria for being a life-extending treatment at the end of life**. • Taking this into account, the **cost-effectiveness estimates** for nivolumab plus ipilimumab were **within the range that NICE normally considers an acceptable use of NHS resources**. So, it is recommended.
Nivolumab + Ipilimumab	CADTH[38]	08/2021: CADTH recommends that **nivolumab plus ipilimumab should be reimbursed** by public drug plans for the treatment of **malignant pleural mesothelioma** to treat patients who have **not received prior systemic treatment** for MPM and who have good performance status at the start of treatment. • Evidence from a clinical trial demonstrated that nivolumab plus ipilimumab **improved overall survival** in adults with unresectable MPM with good performance status and who had not received prior MPM treatment.

		• Based on public list prices, nivolumab plus ipilimumab **is not considered cost-effective** at a willingness to pay of $50,000 per quality-adjusted life-year (QALY) for the indicated population relative to currently reimbursed alternatives. • Economic evidence suggests that **a price reduction of at least 72% is needed** for both nivolumab and ipilimumab to ensure this combination is cost-effective at a $50,000 per QALY threshold. • Based on public list prices, **the 3-year budget impact of nivolumab plus ipilimumab is $72 million**.
Nivolumab + Ipilimumab	IQWIG[39]	08/2021: **First-line treatment** of **unresectable malignant pleural mesothelioma** in adults. • Patients with **epithelioid** tumor histology: **added benefit not proven**. • Patients with **non-epithelioid** tumor histology: **indication of considerable added benefit**.

Conclusion Statement – Nivolumab

In mesothelioma (pleural/peritoneal), nivolumab is used in the first-line setting in combination with ipilimumab (preferred therapy for (preferred therapy for biphasic or sarcomatoid histology). It is also used as second-line treatment of mesothelioma in combination with ipilimumab (preferred if chemotherapy used in first-line).

The Nivolumab plus Ipilimumab immunotherapy combination has received positive reviews from HAS, NICE, CADTH, and IQWIG in the malignant pleural mesothelioma indication:

- **HAS recommends the reimbursement** of nivolumab + ipilimumab in the **first-line treatment of adult patients with unresectable malignant pleural mesothelioma**, citing a **therapeutic improvement** compared to pemetrexed and platinum-based chemotherapy, a **substantial clinical benefit**, and a **minor clinical added value (CAV IV)**
- **NICE** guidance **recommends** nivolumab + ipilimimab as an option for **untreated unresectable malignant pleural mesothelioma** in adults with performance status 0-1, citing **improved overall survival and progression free survival compared with chemotherapy**, and **meeting NICE's criteria for being a life-extending treatment at the end of life**. The **cost-effectiveness estimates** for nivolumab plus ipilimumab were **within the**

range that NICE normally considers an acceptable use of NHS resources.

- CADTH recommends that **nivolumab plus ipilimumab should be reimbursed** by public drug plans for the treatment of **malignant pleural mesothelioma** to treat patients who have **not received prior systemic treatment** for MPM and who have good performance status. The committee cites that nivolumab plus ipilimumab **improved overall survival** in adults with unresectable MPM with good performance status and who had not received prior MPM treatment. However, nivolumab plus ipilimumab **is not considered cost-effective** at a willingness to pay of $50,000 per QALY for the indicated population relative to currently reimbursed alternatives. **A price reduction of at least 72% is needed** for both nivolumab and ipilimumab to ensure this combination is cost-effective at a $50,000 per QALY threshold.
- For **IQWIG**, the added benefit of the combination nivolumab + ipilimumab depends on the **tumor histology**. In patients with **epithelioid** tumor histology the **added benefit of the combination is not proven**, while in patients with **non-epithelioid** tumor histology there's an **indication of considerable added benefit**. This aligns with the NCCN preferred treatment recommendations stated for each histological subtype.

2.5 Topoisomerase Inhibitors

2.5.1 Doxorubicin

Table 20. Doxorubicin Drug Information

Scientific Name Doxorubicin[41]	
Trade Name(s) on Saudi Market	Doxorubicin (Ebewe, Accord), Adriablastina
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2004
FDA approved / off label	Yes, 1974
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C45.1
Drug Class	Antineoplastic agent
Drug Sub-class	Anthracycline; Topoisomerase II inhibitor
SFDA Registration Number (New)	Doxorubicin Ebewe: 4-355-01 (10mg); 5-355-01 (50mg);

	39-355-07 (100mg) Doxorubicin Accord: 5-5223-18 (10mg); 6-5223-18 (50mg) Adriablastina: 6-5669-22 (10mg); 7-5669-22 (50mg)
ATC Code	L01DB01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**HIPEC Cisplatin+Doxorubicin regimen:** Cisplatin 50 mg/m^2 Doxorubicin 15 mg/m^2 (based on case-report data)[27]
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl <10 mL/minute: No need for adjustment - Hemodialysis: Consider administering 75% of the original dose Hepatic Impairment (Adult): - Serum bilirubin 1.2 to 3 mg/dL: Administer 50% of dose. - Serum bilirubin 3.1 to 5 mg/dL: Administer 25% of dose. - Severe hepatic impairment (Child-Pugh class C or bilirubin >5 mg/dL): Use is contraindicated. **Not applicable for IP therapy**
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used concurrently with cisplatin
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Cumulative lifetime limit: 400 mg/m^2 (**Not applicable for IP therapy)**
ST (Step Therapy)	First-line treatment of PeM as part of HIPEC regimens in combination with

	cisplatin for the management of selected cases (unicavitary PeM and epithelioid histology who are medically operable if a complete cytoreduction is achievable). Cisplatin/Doxorubicin is cited to be the preferred regimen in this indication
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Cumulative lifetime limit: 400 mg/m^2 (**Not applicable for IP therapy)**
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions **(Most common and most serious)**	- Most common: Acute cardiotoxicity, malaise, alopecia, discoloration of sweat, pruritus, skin photosensitivity, skin rash, urticaria, amenorrhea, dehydration, hyperuricemia, abdominal pain, anorexia, diarrhea, discoloration of saliva, gastrointestinal ulcer, metastatic urothelial carcinomaositis, nausea, vomiting, urine discoloration, infertility, leukopenia, neutropenia, anemia, thrombocytopenia, weakness, discoloration of tears - Most serious: Acute cardiotoxicity (Atrioventricular block, bradycardia, bundle branch block, ECG abnormality, extrasystoles, nonspecific ST or T wave changes on ECG, sinus tachycardia, supraventricular tachycardia, tachyarrhythmia, ventricular tachycardia), Delayed cardiotoxicity (cardiac failure, decreased left ventricular ejection fraction, myocarditis, pericarditis)
Drug Interactions*	- Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, CYP2D6 Inhibitors/Inducers, Deucravacitini

	b, Dipyrone, Fexinidazole, Filgotinib, Lasmiditan, Nadofaragen, Natalizumab, Pacritinib, P-glycoprotein/ABCB1 Inducers/Inhibitors, Pimecrolimus, Ritlecitinib, Ruxolitinib (Topical), Sparsentan, Tacrolimus (Topical), Talimogene Laherparepvec, Taurursodiol, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Ado-Trastuzumab Emtansine, COVID-19 Vaccine, Deferiprone, Denosumab, Erdafitinib, Influenza Virus Vaccines, Fam-Trastuzumab Deruxtecan, Leflunomide, Lenograstim, Lipegfilgrastim, Margetuximab, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Trastuzumab, Vaccines (Inactivated/Non-Replicating), Zidovudine
Special Population	Pediatrics, Radiation recipients
Pregnancy	Pregnancy Category D: Not used in pregnancy. Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Doxorubicin and its metabolites are present in breast milk. The manufacturer does not recommend breastfeeding during doxorubicin therapy and for 10 days after the last doxorubicin dose.
Contraindications	Severe hypersensitivity to doxorubicin or any component of the formulation; recent myocardial infarction (within past 4 to 6 weeks), severe myocardial insufficiency; severe persistent drug-induced myelosuppression; severe

	hepatic impairment (Child-Pugh class C or bilirubin >5 mg/dL).
Monitoring Requirements	- Cumulative (lifetime) anthracycline/doxorubicin dose - CBC with differential and platelet count - LFTs (bilirubin, ALT/AST, alkaline phosphatase; renal function (creatinine), serum uric acid, and electrolytes (calcium, potassium, phosphate) - Assess cardiac function: ECG, left ventricular ejection fraction increase the frequency of assessments as the cumulative dose exceeds 300 mg/m^2) - Pregnancy status prior to use - Monitor hydration status and for signs/symptoms of tumor lysis syndrome and secondary malignancies - Monitor infusion site
Precautions	- Bone marrow suppression - Cardiomyopathy - Extravasation: Vesicant - Secondary malignancy - Tumor lysis syndrome - Hepatic impairment: - Special populations - Pediatric - Radiation recipients - Formulations (conventional vs liposomal)
Black Box Warning	- Cardiomyopathy - Extravasation - Secondary malignancy - Immunosuppression
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for doxorubicin in mesothelioma.

Conclusion Statement – Doxorubicin

In peritoneal mesothelioma, doxorubicin is used in combination with cisplatin in HIPEC regimens for the management of selected cases of peritoneal mesothelioma (unicavitary PeM and epithelioid histology who are medically operable if a complete cytoreduction is achievable). Cisplatin/Doxorubicin is cited to be the preferred regimen in this indication.

There is no data issued by HTA bodies regarding its use.

2.6 Vascular Endothelial Growth Factor (VEGF) Inhibitors

2.6.1 Bevacizumab

Table 21. Bevacizumab Drug Information

Scientific Name Bevacizumab[42]	
Trade Name(s) on Saudi Market	Avastin; Zirabev; Mvasi
SFDA Classification	Prescription
SFDA Approved Indication	Yes
FDA approved/off label	Yes
EMEA approved/off label	Yes
MHRA approved/off label	Yes
PMDA approved/off label	Yes
Indication (ICD-10)	C45
Drug Class	Antineoplastic agent, monoclonal antibody
Drug Sub-Class	Vascular Endothelial Growth Factor (VEGF) Inhibitor
SFDA Registration Number (New)	Avastin 100mg: 269-24-14 Avastin 400mg: 270-24-14 Zirabev 100mg: 2411200290 Zirabev 400mg: 2411200291 Mvasi 100mg: 2402210547 Mvasi 400mg: 2402210550
ATC Code	L01XC07
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Malignant pleural mesothelioma, unresectable:** 15 mg/kg every 3 weeks

	(in combination with pemetrexed and cisplatin) for up to 6 cycles, followed by bevacizumab maintenance therapy at 15 mg/kg once every 3 weeks until disease progression or unacceptable toxicity
Dose (Pediatric)	N/A
Adjustment	Renal impairment prior to treatment: No dosage adjustment Renal impairment during treatment: - Nephrotic syndrome (proteinuria >3.5 g per 24 hours): discontinue bevacizumab and refer to a kidney specialist. - Proteinuria ≥2 to ≤3.5 g per 24 hours: Withhold bevacizumab and resume therapy if and when urine protein levels are <2 g per 24 hours. Hepatic impairment prior to or during treatment: No dosage adjustment
Prescribing Edits*	CU, MD, QL, ST, PE
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with cisplatin/pemetrexed or with atezolizumab (only in peritoneal mesothelioma)
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose: 15 mg/kg
ST (Step Therapy)	First-line treatment of pleural and peritoneal mesothelioma in combination with cisplatin/pemetrexed (preferred therapy for epitheliod histology). Second-line treatment of pleural and peritoneal mesothelioma in combination with cisplatin/pemetrexed (preferred if nivolumab/ipilimumab used in first-line).

	Second-line treatment of **peritoneal** mesothelioma in combination with atezolizumab (other recommended options).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	15 mg/kg/day
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: increased ALTs, increased alkaline phosphatase, thrombocytopenia, leukopenia, hypoalbuminemia, hyponatremia, hypocalcemia, hyperglycemia, hypertension - Most serious: nephrotic syndrome
Drug Interactions*	Anthracyclines: enhanced cardiotoxicity (risk X) Cladribine, dipyrone, fexinidazole: enhanced myelosuppressive effect (risk X) Sunitinib: increased risk of microangiopathic hemolytic anemia (risk X)
Special Population	Patients ≥ 65 years of age have an increased incidence of arterial thrombotic events.
Pregnancy	Based on findings in animal reproduction studies and on the mechanism of action, bevacizumab may cause fetal harm if administered during pregnancy. Information from post-marketing reports following systemic exposure in pregnancy is limited.
Lactation	It is not known if bevacizumab is present in breast milk.
Contraindications	Known hypersensitivity to the product or its components
Monitoring Requirements	Proteinuria/nephrotic syndrome Blood pressure Pregnancy status

	HBV screening prior to initiation (do not delay treatment for screening results)
Precautions	- GI perforation/fistula - Heart failure - Hemorrhage - Hypertension - Infusion reactions - Necrotizing fasciitis - Osteonecrosis of the jaw - Ocular adverse events - Posterior reversible encephalopathy syndrome - Proteinuria/nephrotic syndrome - Wound healing complications - Thromboembolism
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for bevacizumab in mesothelioma.

Conclusion Statement – Bevacizumab

In mesothelioma (pleural/peritoneal), bevacizumab is used in the first-line setting in combination with cisplatin/pemetrexed (preferred therapy for epitheliod histology). It is also used as second-line treatment of mesothelioma in combination with cisplatin/pemetrexed (preferred if nivolumab/ipilimumab used in first-line) or in combination with atezolizumab (for peritoneal mesothelioma).

There is no data issued by HTA bodies regarding its use.

2.6.2 Ramucirumab

Table 22. Ramucirumab Drug Information

Scientific Name Ramucirumab[43]	
Trade Name(s) on Saudi Market	Cyramza
SFDA Classification	Prescription
SFDA Approved Indication	Yes; used off-label in mesothelioma
FDA approved/off label	Yes; used off-label in mesothelioma

EMEA approved/off label	Yes; used off-label in mesothelioma
MHRA approved/off label	Yes; used off-label in mesothelioma
PMDA approved/off label	Yes; used off-label in mesothelioma
Indication (ICD-10)	C45.0
Drug Class	Antineoplastic agent, monoclonal antibody
Drug Sub-Class	Vascular Endothelial Growth Factor (VEGF) Inhibitor
SFDA Registration Number (New)	1307233869 (100 mg) 1307233868 (500 mg)
ATC Code	L01XC21
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	10 mg/kg on day 1 every 21 days
Dose (Pediatric)	N/A
Adjustment	Hepatic Impairment (Adult): Severe impairment (total bilirubin >3 times ULN and any AST): No dosage adjustments provided in the manufacturer's labeling (has not been studied). Use in patients with Child-Pugh class B or C cirrhosis only if the potential benefits of treatment outweigh the potential risks of clinical deterioration.
Prescribing Edits*	AGE, MD, ST, CU, PE, QL
AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	Used in combination with gemcitabine
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose: 10 mg/kg
ST (Step Therapy)	Second-line treatment of **pleural** mesothelioma in combination with gemcitabine (other recommended options).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol

Maximum Daily Dose Adults*	10 mg/kg/day
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Hypertension, peripheral edema, hypoalbuminemia, hypocalcemia, hyponatremia, abdominal pain, decreased appetite, diarrhea, nausea, proteinuria, neutropenia, thrombocytopenia, ascites, fatigue, headache, insomnia, epistaxis - Most serious: Arterial thromboembolism, Intestinal obstruction, hepatic encephalopathy, hepatorenal syndrome, acute myocardial infarction, hemorrhage, cerebral ischemia, cerebrovascular accident
Drug Interactions*	Risk C: Androgens, Bisphosphonates, Efgartigimod, Rozanolixizumab, Solriamfetol
Special Population	Patients ≥ 65 years of age
Pregnancy	Pregnancy Category C
Lactation	It is not known if ramucirumab is present in breast milk. Immunoglobulins are excreted in breast milk, and it is assumed that ramucirumab may appear in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during treatment and for 2 months after the final ramucirumab dose.
Contraindications	N/A
Monitoring Requirements	- LFTs - Urine protein - Thyroid function - CBC with differential - Pregnancy status - Monitor BP; Comprehensive cardiac assessment before treatment; ECG

	- Monitor for signs/symptoms of infusion-related reactions - Monitor for signs/symptoms of arterial thromboembolic events, bleeding/hemorrhage, GI perforation, wound healing impairment, and posterior reversible encephalopathy syndrome
Precautions	- Arterial thrombotic events - Gastrointestinal perforation - Hemorrhage - Hepatotoxicity - Hypertension - Infusion reaction - Posterior reversible encephalopathy syndrome - Proteinuria/Nephrotic syndrome - Thyroid dysfunction - Wound healing impairment:
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for ramucirumab in mesothelioma.

Conclusion Statement – Ramucirumab

In mesothelioma, ramucirumab is used in the second-line of **pleural** mesothelioma in combination with gemcitabine.

There is no data issued by HTA bodies regarding its use.

Section 3.0 Key Recommendations Synthesis

Patients with mesothelioma are managed by a multidisciplinary team with experience in mesothelioma[2,18,23].

A. Pleural Mesothelioma

a. Surgery

Surgery is recommended for certain patients with clinical stage I to IIIA MPM and epithelioid histology. Surgery may be considered for certain patients with early-stage MPM who have biphasic histology. However, surgery is generally not an option for those with stage IIIB or IV MPM regardless of histology. It is essential that patients receive a careful assessment before surgery is performed[2,19,20,22,23].

Surgical resection for patients with MPM can include either:

1. Pleurectomy/decortication (P/D; also known as total pleurectomy, lung-sparing surgery), which is complete removal of the involved pleura and all gross tumor with or without en-bloc resection of the pericardium and/or diaphragm; or
2. Extrapleural pneumonectomy (EPP), which is en-bloc resection of the involved pleura, lung, ipsilateral diaphragm, and often the pericardium.

Extended P/D refers to the resection of the diaphragm and pericardium in addition to total pleurectomy. Mediastinal nodal dissection is recommended in patients having either P/D or EPP; at least 3 nodal stations should be obtained[2,19,20,22,23].

b. Systemic Therapy

Chemotherapy is recommended as part of a **multimodality regimen** for patients with **medically operable** MPM. Patients with **medically operable stage I to IIIA MPM** can receive chemotherapy either before or after surgery (Recommendation Level A, Evidence Level II)[2,19,20,22,23].

Systemic therapy alone is recommended for patients with[2,19,20,22,23]:

1. **Stage IIIB or IV MPM (PS 0–2)** regardless of histology;
2. Those with **sarcomatoid** or **biphasic** histology, regardless of clinical stage. It is important to note that cases like biphasic or sarcomatous histology should still be discussed in MDT where surgery may be considered; or
3. **Medically inoperable** stages I to IV MPM, or those who refuse surgery (Recommendation Level A, Evidence Level II).

All of the regimens recommended for MPM can also be used for **malignant peritoneal mesothelioma**, **pericardial mesothelioma**, and **tunica vaginalis testis** mesothelioma[2,19,20,22,23].

b.1 Medically Operable MPM

Preoperative (induction) chemotherapy with **pemetrexed plus (cisplatin or carboplatin)** is recommended for eligible patients with *resectable MPM* (Recommendation Level A, Evidence Level II). **Postoperative chemotherapy** is also recommended if patients *have not received induction chemotherapy* (Recommendation Level A, Evidence Level II)[2,19,20,22,23].

b.2 Medically Inoperable MPM

b.2.1 First-Line Therapy

- **Nivolumab plus ipilimumab** immunotherapy is recommended for eligible patients with unresectable MPM based on clinical trial data and the FDA approval (Recommendation Level A, Evidence Level II). It is the **preferred** option for patients with **biphasic or sarcomatoid histology**[2,19,20,22,23].
    - Testing for PD-L1 is not required for prescribing nivolumab for therapy for patients with MPM.
    - Immune-related adverse events, such as pneumonitis, may occur with nivolumab plus ipilimumab. Intravenous high-dose corticosteroids should be administered based on the severity of the reaction for patients with immune-mediated adverse events.
    - Nivolumab plus ipilimumab should be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated.
    - Ipilimumab can also cause immune-mediated adverse events such as hepatitis and endocrinopathies[2].
- **Cisplatin/Pemetrexed** is recommended for patients with MPM based on clinical trial data and the FDA approval (Recommendation Level A, Evidence Level I). It's a **preferred** first-line treatment option in patients with **epitheliod histology**[2,19,20,22,23].
    - **Carboplatin/Pemetrexed** is an alternative treatment option based on clinical trial data in patients who are not eligible for cisplatin (Recommendation Level A, Evidence Level II)[2].
- **Cisplatin/Pemetrexed/Bevacizumab** followed by **Bevacizumab maintenance** is a treatment option for bevacizumab-eligible patients with unresectable MPM regardless of histology (Recommendation Level A, Evidence Level I). It's also a **preferred** first-line treatment option in patients with **epitheliod histology**[2,19,20,22,23].
    - Contraindications to bevacizumab include uncontrolled hypertension, risk for bleeding or clotting, and substantial cardiovascular morbidity.

- An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
- **Bevacizumab** can be added to carboplatin/pemetrexed with or without maintenance bevacizumab as a first-line therapy option for patients with unresectable MPM (Recommendation Level A, Evidence Level I)[2,19,20,22,23].

- **Gemcitabine/cisplatin** is a treatment option for eligible patients with unresectable MPM (Recommendation Level A, Evidence Level II)[2,19,20,22,23].
- Other first-line options include **pemetrexed** or **vinorelbine** for patients who are *not candidates* for platinum-based combination therapy (Recommendation Level A, Evidence Level I)[2,19,20,22,23].

b.2.2 Subsequent Systemic Therapy

The following are recommended subsequent therapy options for patients with MPM (if not administered first line)[2,19,20,22,23]:

1. **Pemetrexed** (Recommendation Level A, Evidence Level I). It's a preferred subsequent treatment option if immunotherapy was given in first line; or
2. **Pemetrexed/(Cisplatin or Carboplatin) ± Bevacizumab** (Recommendation Level A, Evidence Level I). It's a preferred subsequent treatment option if immunotherapy was given in first line; or
3. **Nivolumab** with (or without) **Ipilimumab** (Recommendation Level A, Evidence Level II). It's the preferred subsequent treatment option if chemotherapy was given in first line.

Other subsequent chemotherapy options include[2,19,20,22,23]:

1. **Rechallenging** with **pemetrexed-based regimens** if patients had a good, sustained response to first-line therapy (Recommendation Level A, Evidence Level II);
2. **Vinorelbine** (Recommendation Level A, Evidence Level II); or
3. **Gemcitabine ± Ramucirumab** (Recommendation Level A, Evidence Level II)[2]

c. Radiation Therapy

In patients with MPM, RT can be used as part of a multimodality regimen; however, RT alone is not recommended for treatment. RT can also be used as palliative therapy for relief of chest pain, bronchial or esophageal obstruction, or other symptomatic sites associated with MPM, such as metastases in bone or in the brain[2,19,20,22,23].

The dose of radiation should be based on the purpose of treatment. The most appropriate timing of delivering RT (i.e., after surgical intervention, with [or without] chemotherapy) should be discussed with a multidisciplinary team. After EPP, adjuvant hemithoracic RT may reduce the local recurrence rate. Patients are

candidates for RT if they have good PS, pulmonary function, and kidney function[2,19,20,22,23].

In patients with limited or no resection of disease (i.e., in the setting of an intact lung), high-dose conventional RT to the entire hemithorax has not been shown to improve survival and is associated with significant toxicity[2].

- Hemithoracic pleural Intensity-modulated radiation therapy (IMRT) can be considered following induction chemotherapy and P/D in certain patients with MPM if done in centers with expertise in this technique.
- Prophylactic RT is not routinely recommended to prevent instrument-tract recurrence after pleural intervention based on the SMART trial.
- Hemithoracic pleural IMRT is not recommended after EPP.

B. Peritoneal Mesothelioma

Treatment options for patients with diffuse PeM include **surgery** and/or **systemic therapy**[2,18,21].

- Select patients with medically operable diffuse PeM and good performance status (PS) are candidates for multimodality therapy, including those with epithelioid histology and unicavitary disease.
- **Systemic therapy** is recommended for patients with **diffuse PeM** who are not eligible for or refuse surgery. Best supportive care is recommended for patients with a PS of 3 to 4.
- **Radiation therapy** is not recommended as a primary therapy for PeM but can be used selectively for **palliation**.

Treatment options for patients with peritoneal inclusion cyst or well-differentiated papillary mesothelial tumor (WDPMT) include[2,18,21]:

1. Observation with imaging surveillance for those with asymptomatic and noninvasive disease; or
2. Cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) for those who have symptomatic, recurrent, or microinvasive disease.

There are no phase 3 randomized trials to determine the best treatment for patients with PeM because it is so rare, although there are a few clinical trials. Because PeM and pleural mesothelioma are similar, systemic therapy recommendations for PeM are based on extrapolating data from clinical trials in **pleural mesothelioma**; recommendations are also based on clinical trials in PeM, and on the expertise of the panel members[2].

a. Surgery and Intraperitoneal Chemotherapy

Cytoreductive surgery (CRS) and **Hyperthermic intraperitoneal chemotherapy** (HIPEC) are possible for eligible patients with PeM. Appropriate patients should be evaluated by surgeons, medical oncologists, and diagnostic imaging specialists to assess if they are candidates for multimodality treatment[2,18,21].

Complete cytoreduction and HIPEC are recommended for patients with **unicavitary PeM** and **epithelioid histology** who are medically operable if a complete cytoreduction is achievable. **Perioperative systemic therapy** should be considered if patients have **high-risk features** (such as Ki-67 >9%, nodal metastases, high tumor burden [peritoneal cancer index >17]), completeness of cytoreduction (CC) > 1, biphasic disease, or bicavitary disease). Although measuring the Ki-67 index is not routinely recommended at diagnosis, it may be useful for helping to define high-risk features. After perioperative therapy, patients may be eligible for CRS and HIPEC[2,18,21].

Intraperitoneal chemotherapy regimens and stratified as per below[2,18,21]:

1. Cisplatin plus doxorubicin;
2. Cisplatin;
3. Carboplatin; or
4. Cisplatin plus mitomycin

Monotherapy mitomycin regimens are useful in certain circumstances[2].

b. Systemic Therapy

Systemic therapy alone is recommended for patients with a PS of 0 to 2 and diffuse PeM, including those who[2,18,21]:

1. who are medically **inoperable**, for whom a complete CRS cannot be achieved, or who refuse surgery;
2. with **bicavitary disease** regardless of histology and stage;
3. with **sarcomatoid** or **biphasic histology** regardless of stage; or
4. with **recurrence** after previous CRS and HIPEC.

Surgery may be considered in select patients with bicavitary disease or low-volume biphasic disease. The systemic therapy regimens are also recommended for eligible patients with pleural mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma[2].

Preferred first-line systemic therapy regimens for eligible patients with **PeM** and **epithelioid histology** who are not eligible for surgery and are[2,18,21]:

1. **Pemetrexed/Cisplatin/Bevacizumab** (Recommendation Level A, Evidence Level II)
2. **Pemetrexed/cisplatin** (Recommendation Level A, Evidence Level II)

3. **Nivolumab/Ipilimumab** (Recommendation Level A, Evidence Level II)

The **preferred first-line** systemic therapy regimens for eligible patients with **PeM** and **biphasic or sarcomatoid histology** who are not eligible for surgery is **nivolumab plus ipilimumab** (Recommendation Level A, Evidence Level II)[2,18,21].

The following are other recommended regimens for biphasic or sarcomatoid histology[2,18,21]:

1. **Pemetrexed/Cisplatin/Bevacizumab** (Recommendation Level A, Evidence Level II)
2. **Pemetrexed/Cisplatin** (Recommendation Level A, Evidence Level II)

The following regimens are useful in certain circumstances (all histologies)[2,18,21]:

1. **Gemcitabine/Cisplatin** (Recommendation Level A, Evidence Level II)
2. **Pemetrexed** (Recommendation Level A, Evidence Level II)
3. **Vinorelbine** (Recommendation Level A, Evidence Level II).

Carboplatin is recommended if patients are **not candidates for cisplatin**, regardless of histology (Recommendation Level A, Evidence Level II)[2].

Preferred subsequent (second-line and beyond) **systemic therapy** regimens for eligible patients with **PeM**, regardless of histology, if they were not given first line are[2,18,21]:

1. **Pemetrexed/Cisplatin/Bevacizumab** (Recommendation Level A, Evidence Level II)
2. **Pemetrexed/Cisplatin** (Recommendation Level A, Evidence Level II)
3. **Pemetrexed** (Recommendation Level A, Evidence Level II)
4. **Nivolumab/Ipilimumab** (Recommendation Level A, Evidence Level II)

However, pemetrexed regimens may be given again as subsequent systemic therapy if a good, sustained response was obtained when the initial chemotherapy was interrupted[2].

The following are other recommended subsequent therapy regimens[2,18,21]:

1. **Atezolizumab plus Bevacizumab** (Recommendation Level A, Evidence Level II). Atezolizumab plus bevacizumab should only be considered as subsequent therapy if patients have not previously been treated with ICIs[2].
2. **Vinorelbine** (Recommendation Level A, Evidence Level II)
3. **Gemcitabine** (Recommendation Level A, Evidence Level II)

Although about 50% of patients with PeM have positive programed cell death-ligand 1 (PD-L1) expression levels, PD-L1 testing is not required before using ICIs. ICIs are associated with unique immune-mediated adverse events, such as endocrine disorders, that are not seen with traditional cytotoxic chemotherapy; therefore, health care providers should be aware of the spectrum of potential

immune-mediated adverse events, know how to manage the adverse events, and educate their patients about possible side effects. Atezolizumab, nivolumab, or ipilimumab should be discontinued for patients with severe or life-threatening pneumonitis or myocarditis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated-mediated adverse events when indicated[2].

C. HTA Recommendations

HTA recommendations were found for the immunotherapy combination Nivolumab + Ipilimumab as well as for Pemetrexed in malignant pleural mesothelioma (*c.f* section 2).

The Nivolumab plus Ipilimumab immunotherapy combination has received positive reviews from HAS, NICE, CADTH, and IQWIG in the malignant pleural mesothelioma indication[36-39]:

- **HAS recommends the reimbursement** of nivolumab + ipilimumab in the **first-line treatment of adult patients with unresectable malignant pleural mesothelioma**, citing a **therapeutic improvement** compared to pemetrexed and platinum-based chemotherapy, a **substantial clinical benefit**, and a **minor clinical added value (CAV IV)**[36].
- **NICE** guidance **recommends** nivolumab + ipilimimab as an option for **untreated unresectable malignant pleural mesothelioma** in adults with performance status 0-1, citing **improved overall survival and progression free survival compared with chemotherapy**, and **meeting NICE's criteria for being a life-extending treatment at the end of life**. The **cost-effectiveness estimates** for nivolumab plus ipilimumab were **within the range that NICE normally considers an acceptable use of NHS resources**[37].
- CADTH recommends that **nivolumab plus ipilimumab should be reimbursed** by public drug plans for the treatment of **malignant pleural mesothelioma** to treat patients who have **not received prior systemic treatment** for MPM and who have good performance status. The committee cites that nivolumab plus ipilimumab **improved overall survival** in adults with unresectable MPM with good performance status and who had not received prior MPM treatment. However, nivolumab plus ipilimumab **is not considered cost-effective** at a willingness to pay of $50,000 per QALY for the indicated population relative to currently reimbursed alternatives. **A price reduction of at least 72% is needed** for both nivolumab and ipilimumab to ensure this combination is cost-effective at a $50,000 per QALY threshold[38].
- For **IQWIG**, the added benefit of the combination nivolumab + ipilimumab depends on the **tumor histology**. In patients with **epithelioid** tumor histology the **added benefit of the combination is not proven**, while in patients with **non-epithelioid** tumor histology there's an **indication of**

considerable added benefit. This aligns with the NCCN preferred treatment recommendations stated for each histological subtype[39].

Pemetrexed has received positive reviews from HAS and NICE in the malignant pleural mesothelioma indication[31,32]:

- **HAS recommends the reimbursement** of pemetrexed, citing a **substantial actual benefit** and **moderate clinical added value** in **first-line treatment of unresectable malignant pleural mesothelioma**[31].
- **NICE** on the other hand **recommends pemetrexed** as a treatment option for **malignant pleural mesothelioma** only in people who have a World Health Organization (WHO) performance status of 0 or 1, who are considered to have **advanced disease** and for whom **surgical resection is considered inappropriate.** The results of the EMPHACIS trial suggest that **pemetrexed plus cisplatin** confers a **survival benefit of approximately 3 months** compared with **cisplatin alone**, in addition to **advantages** in terms of 1**-year survival, median time to progressive disease, tumor response rate and quality of life.** The economic analyses indicate an incre**mental cost per QALY gained of greater than £60,000** when pemetrexed plus cisplatin was compared with cisplatin alone in the fully supplemented population. Pemetrexed plus cisplatin, when compared with cisplatin alone, appears to have **lower ICERs in patients with advanced disease and/or good performance status**[32].

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of mesothelioma.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Examples:

Age Edit: Desmopressin in Nocturnal Enuresis should not be prescribed for children < 5 years.

Concurrent Use Edit: Flavoxate in Nocturnal Enuresis should be used as add on to desmopressin after desmopressin failure and cannot be used alone.

Gender Edit: Exemestane in Endometriosis should be used only by Females.

Physician Specialty Edit: Fentanyl in Endometriosis should be prescribed by a gynecologist or pain management specialist.

Prior Authorization: Desmopressin in Nocturnal Enuresis: The prescriber must check the following before prescribing: failure of combination of behavioral and alarm therapy

Quantity Limit: Idarubicin in Acute Leukemia: Cumulative dose should not exceed 150 mg/m2. Please note that this Quantity Limit is different than the one

based on maximum daily dose as this is not necessary based on Maximum Daily Dose

Step Therapy: Aripiprazole in Social Anxiety: should be used as third line after: First-line: Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR Second-line: Alprazolam, bromazepam, citalopram, clonazepam, gabapentin

Emergency use only: Furosemide IV form in Hypertension is used only in emergency setting.

Protocol edit: Bendamustine Hydrochloride, Cyclophosphamide, Ifosfamide, Dacarbazine should be used in Lymphoma as per the following protocol

II. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose. If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

III. What information are available in the notes?

“Notes” section provides details of the prescribing edits, extra important drug information and special warning and precautions.

IV. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

V. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

VI. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B Level of Evidence Description

I- Level of Evidence Adopted:

Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

II. NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category C	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

All recommendations are category 2A unless otherwise indicated.

III. NCCN Categories of Preference

Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

Appendix C. MeSH Terms PubMed

The following is the result of the PubMed search conducted for mesothelioma guideline search:

Query	Filters	Search Details	Results
(((((Mesothelioma [Title/Abstract]) OR (Mesothelioma[MeSH Major Topic])) OR (Mesothelioma, Malignant[MeSH Major Topic])) OR (Mesothelioma, Malignant[Title/Abstract])) OR (Mesothelioma, Cystic[Title/Abstract])) OR (Mesothelioma, Cystic[MeSH Major Topic])	Guideline, in the last 5 years	("Mesothelioma "[Title/Abstract] OR " Mesothelioma "[MeSH Major Topic] OR " Mesothelioma, Malignant "[MeSH Major Topic] OR ("Mesothelioma, Malignant "[Title/Abstract]) OR "c Mesothelioma, Cystic "[Title/Abstract] OR " Mesothelioma, Cystic "[MeSH Major Topic]) AND ((y_5[Filter]) AND (guideline[Filter]))	7

Appendix D. Treatment Algorithms

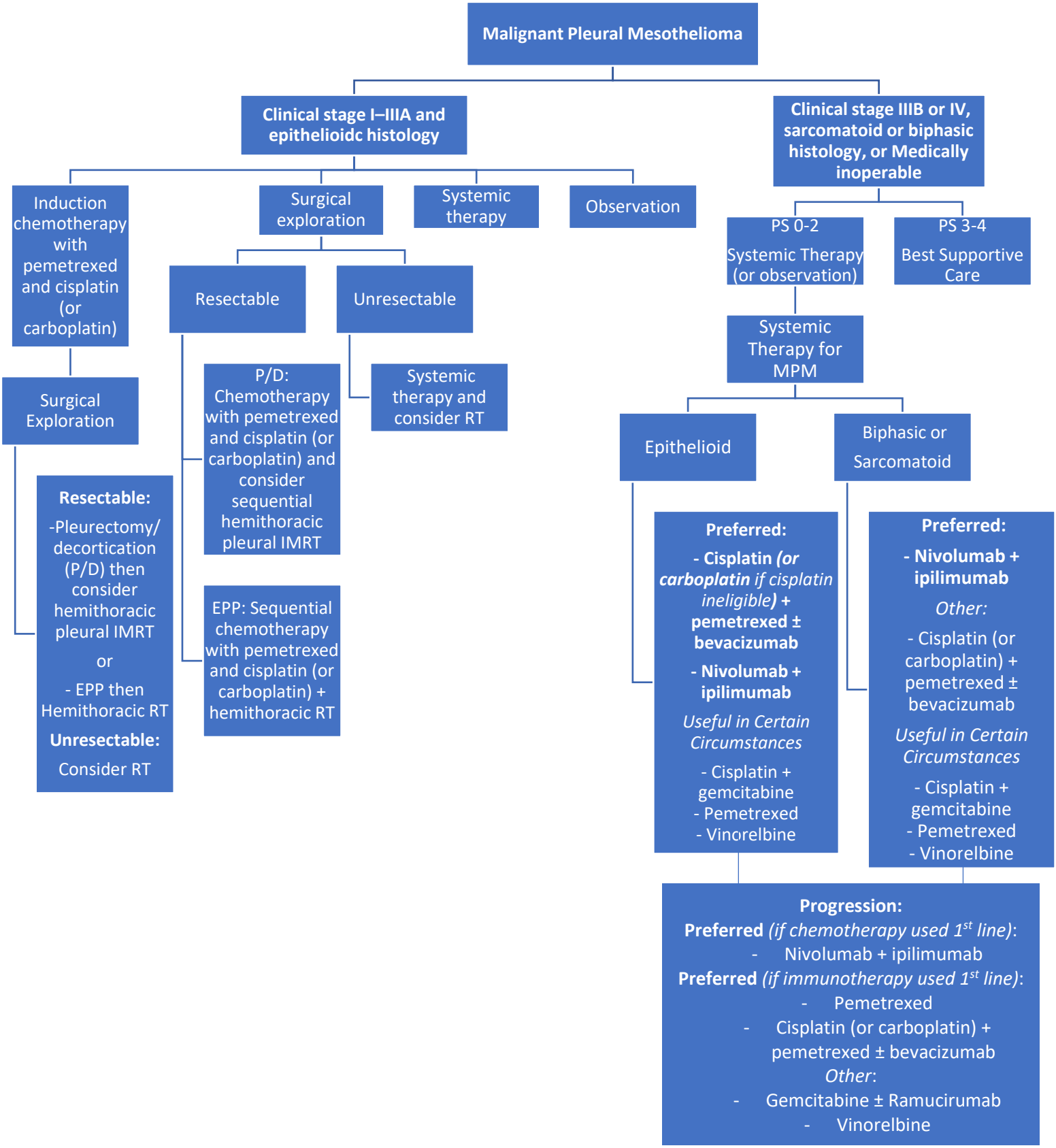

Figure 4. *Management of malignant pleural mesothelioma*

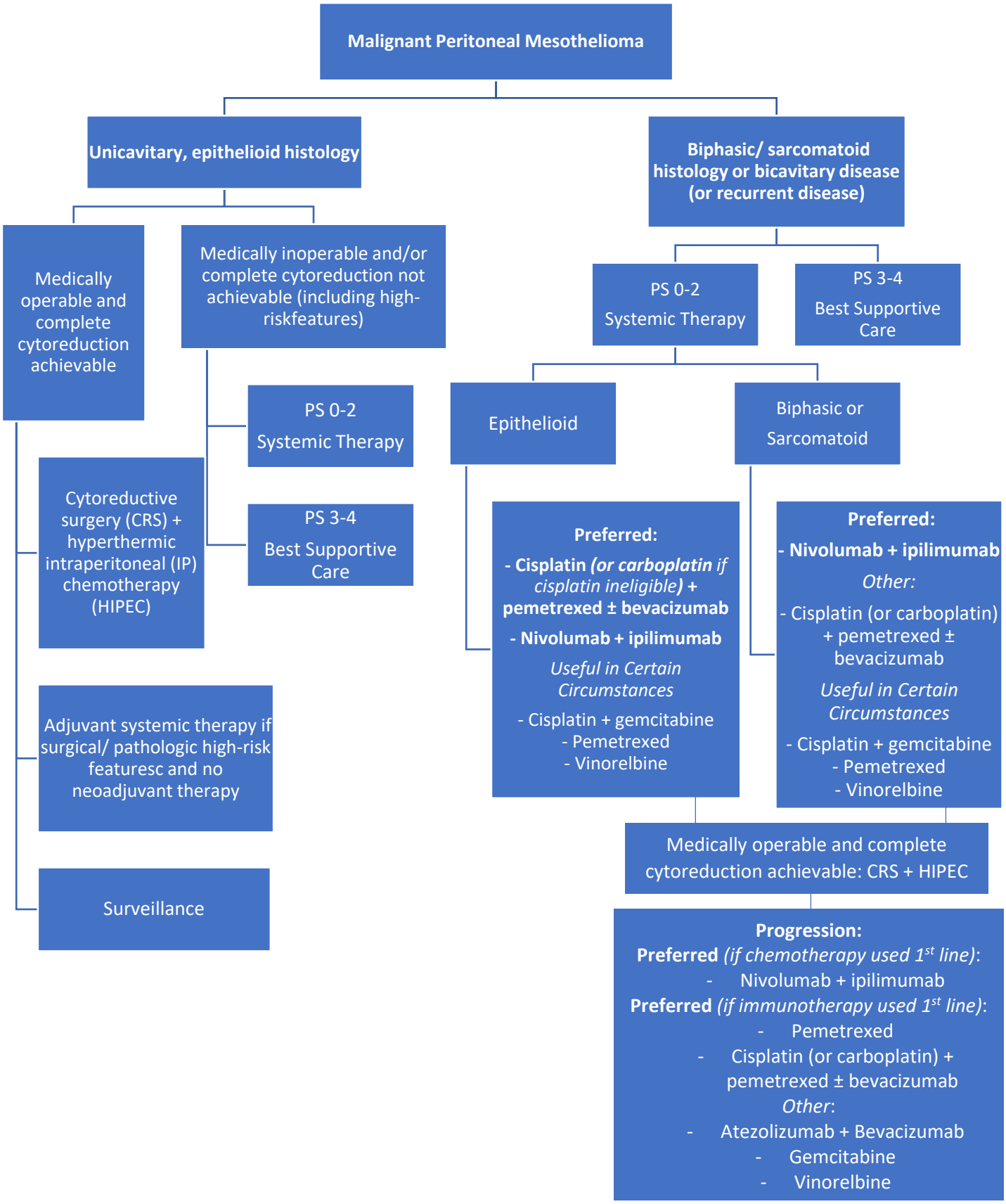

Figure 5. *Management of malignant peritoneal mesothelioma*