NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL
Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Bristol-Myers Squibb Pharmaceuticals

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Mesothelioma UK *(endorsed by patient expert, Leah Taylor)*
   b. Royal College of Pathologists

4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from Bristol-Myers Squibb Pharmaceuticals

7. **Technical engagement responses & expert statements from experts:**
   a. Prof Richard Attanoos – clinical expert, nominated by Royal College of Pathologists
   b. Richard Lech – patient expert, nominated by Mesothelioma UK
   c. Dr Toby Talbot – clinical expert, nominated by Bristol-Myers Squibb Pharmaceuticals

8. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews
   a. ERG Technical Engagement Response
   b. Addendum 1

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma (ID1609)

Document B

Company evidence submission

18 February 2021

File name	Version	Contains confidential information	Date
ID1609_NivoIpi_1LMPM_DocB_FINAL_18Feb2021_redacted	Version 4	No	18 February 2021

Contents

Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission covers the full anticipated marketing authorisation for nivolumab in combination with ipilimumab (nivolumab + ipilimumab) for the proposed indication of first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM). The company submission is consistent with the final National Institute for Health and Care Excellence (NICE) scope and the NICE reference case (Table 1).

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated unresectable MPM	As per the scope	
Intervention	Nivolumab with ipilimumab	As per the scope	
Comparator(s)	• Pemetrexed with cisplatin • Raltitrexed with cisplatin (for people for whom treatment with pemetrexed is unsuitable) • Pemetrexed with carboplatin (for people for whom treatment with cisplatin is unsuitable) • Best supportive care	• Pemetrexed with cisplatin or carboplatin	In CheckMate-743, participants were randomised 1:1 to either open-label nivolumab + ipilimumab or pemetrexed + cisplatin or carboplatin. The choice of cisplatin or carboplatin was the investigator's choice, and the use of cisplatin was preferred; however, carboplatin was used at the discretion of the investigator, and switching from cisplatin to carboplatin and vice versa were allowed if reported in the case report form. For these reasons, pemetrexed + cisplatin or carboplatin is the comparator in this submission, and results for pemetrexed + cisplatin or pemetrexed + carboplatin are not reported separately. Raltitrexed is not approved for use in the UK for the first-line treatment of MPM and is not used in the NHS according to UK registry data (see Section B.1.3.4.1), as well as the UK clinical experts we have consulted (Appendix N) and the scope consultation comments from the British Thoracic Oncology Group. For these reasons, BMS have not included raltitrexed as a comparator in this submission. Best supportive care is also not included as a comparator in this submission. This is because first-line systematic anticancer therapies are only used in patients with good PS (0-1), in accordance with BTS guidelines.[1] In line with clinical practice and the NICE recommendation for pemetrexed,[2] the eligibility criteria of CheckMate-743 only included patients with an ECOG PS of 0-1. According to the UK clinical experts we have consulted (Appendix N) and the scope consultation comments from the British Thoracic Oncology Group, best supportive care is not an appropriate comparator because this technology relates to a particular group of fit patients for whom best supportive care would not be deemed acceptable or ethical unless specifically requested by the patient.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	As per the scope	
Subgroups to be considered	• Histologic subtype (epithelioid, sarcomatoid, biphasic) • Level of PD-L1 expression	• Histology: epithelioid and non-epithelioid • PD-L1 expression: ≥ 1% or < 1%	Clinical efficacy data are presented for the prespecified subgroup analyses in CheckMate-743, which included histology and PD-L1 expression subgroups as per the scope.
Special considerations, including issues related to equity or equality	None	BMS are not aware of specific equality issues for this appraisal. However, MPM is a preventable, occupational-related disease caused by asbestos exposure. BMS wish to highlight that MPM incidence rates vary across England, with higher rates in areas of heavy industry (e.g., the northeast and southern England). Also, as MPM is a rare cancer, patients may be referred in the NHS to a limited number of specialist mesothelioma multidisciplinary teams,[3] which may require patients to travel long distances from their homes for appointments if they live in a rural setting. Patients with MPM are often older and diagnosed at a late stage of the disease. Consequently, they can be too frail to travel for treatment, which may limit their treatment options.	

BMS = Bristol-Myers Squibb; BTS = British Thoracic Society; ECOG = Eastern Cooperative Oncology Group; MPM = malignant pleural mesothelioma; NHS = National Health Service; PD-L1 = programmed death-ligand 1; PS = performance status; UK = United Kingdom.

Sources: Bristol-Myers Squibb[4]; NHS England[3]

B.1.2 Description of the technology being appraised

Nivolumab (Opdivo®; Bristol-Myers Squibb) in combination with ipilimumab (Yervoy®; Bristol-Myers Squibb) for untreated unresectable MPM does not currently have marketing authorisation in the United Kingdom (UK). A summary of the product description of nivolumab + ipilimumab is presented in Table 2 and detailed in the following subsections. In addition, the following document is included in Appendix C in support of this appraisal:

- Draft Summary of Product Characteristics (SmPC)

Table 2. Technology being appraised

UK approved name and brand name	Nivolumab (Opdivo®) with ipilimumab (Yervoy®)
Mechanism of action	Ipilimumab and nivolumab are both fully human, monoclonal immunoglobulin antibodies (IgG1k and IgG4 human monoclonal antibodies, respectively) that act as checkpoint inhibitors of CTLA-4 and PD-1 at their distinct, yet complementary, positions within the T-cell response pathway[5,6]: • Ipilimumab switches off the negative regulation of the immune response (by blocking CTLA-4 [expressed on T-cells] signalling), thus allowing further activation and expansion of the early T-cell response and increasing the number of antigen-specific activated T-cells surrounding the tumour.[5,7-10] • Nivolumab blocks PD-1, an inhibitory receptor expressed on activated T-cells, thus reversing immune suppression and increasing T-cell activation. Therefore, nivolumab allows active T-cells to infiltrate and destroy the tumour, promoting antitumour immunity.[6,11-14] The mechanisms of action of ipilimumab and nivolumab are distinct and complementary, with ipilimumab working early in the immune response by potentiating the presentation of antigens to naive T-cells in the lymph nodes and nivolumab working later in the immune response to increase tumour-specific effector T-cells.[15] Therefore, nivolumab + ipilimumab potentiates immune-mediated tumour destruction, stimulating the patient's own immune system to directly fight cancer cells (in the same way that it would any other foreign cell), which results in destruction of the tumour through pre-existing, intrinsic processes.
Marketing authorisation/CE mark status	A marketing authorisation application has been filed in Europe for nivolumab in combination with ipilimumab for the first-line treatment of adult patients with unresectable MPM.[16,17] It has been studied in a clinical trial (CheckMate-743) compared with PDC (pemetrexed + cisplatin or carboplatin) in adults with untreated unresectable MPM.[18,19] • Regulatory submission was on [redacted] • CHMP opinion is expected in [redacted] • Regulatory approval and marketing authorisation are expected in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The licence application is for nivolumab in combination with ipilimumab for the first-line treatment of adult patients with unresectable MPM.[16,17]
Method of administration and dosage	Intravenous infusion of 360 mg nivolumab every 3 weeks + 1 mg/kg ipilimumab every 6 weeks[17]

UK approved name and brand name	Nivolumab (Opdivo®) with ipilimumab (Yervoy®)
Additional tests or investigations	No additional tests or investigations outside current practice are expected.
List price and average cost of a course of treatment	Nivolumab list price per dose: £3,950 Ipilimumab list price per dose: £7,500 Average cost of a course of treatment at list price: [redacted][a]
Patient access scheme (if applicable)	There are simple discount PASs for nivolumab and ipilimumab approved by the Department of Health that are applicable to this appraisal.

CDF = Cancer Drugs Fund; CHMP = Committee for Medicinal Products for Human Use; CTLA-4 = cytotoxic T-lymphocyte antigen-4; IgG = immunoglobulin G; MPM = malignant pleural mesothelioma; PAS = patient access scheme; PD-1 = programmed death-1; PDC = platinum-based doublet chemotherapy; SmPC = summary of product characteristics; UK = United Kingdom.

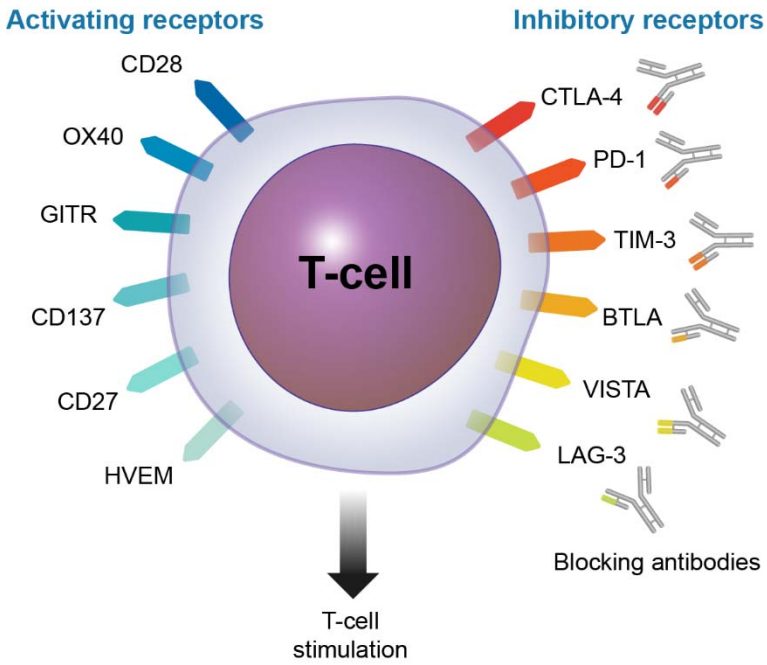
[a] Cost of a course of nivolumab + ipilimumab at list price based on mean number of doses in the CheckMate-743 trial.

B.1.2.1 Nivolumab + ipilimumab: mechanisms of action

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that targets and blocks the programmed death-1 (PD-1) receptor to promote an antitumour immune response. It is administered intravenously.[6,11-14] Ipilimumab is a recombinant human anti–cytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibody that blocks the effects of CTLA-4 to enhance T-cell–mediated immune responses to tumour cells. Ipilimumab is administered intravenously.[5,7-10]

Immunotherapy has been at the forefront of therapeutic development in oncology since the discovery that cancer cells evade destruction by exploiting immune system signalling pathways.[5,6] Neoantigens are novel peptide sequences found on tumour cells that mark them as “non-self” to the immune system; these neoantigens are then detected as “non-self” by circulating antigen-presenting cells (e.g., dendritic cells) which generate an immune response against the foreign cells. The typical immune response to foreign cells in the body is the activation of antigen-specific T-cells that can eradicate them. Discrete populations of T-cells (effectors and regulators) proliferate and differentiate through various pathways, with T-cell activation regulated through a complex balance of positive and negative signals provided by costimulatory receptors on the T-cell surface (Figure 1).[5] Healthy, non-foreign cells (“self-cells”) avoid T-cell destruction by stimulating and displaying inhibitory receptors known as *checkpoints* to suppress the effector T-cell response; cancer cells can use these same inhibitory receptors to escape the immune response. Blocking antibodies designed to bind to these checkpoints (so-called *checkpoint inhibitors*) can prevent tumour-driven T-cell suppression, as depicted in Figure 1, and increase immune activity against cancer cells.[5,6]

Figure 1. Receptors involved in the regulation of the T-cell immune response



BTLA = B- and T-lymphocyte attenuator; CD27 = cluster of differentiation 27; CD28 = cluster of differentiation 28; CD137 = cluster of differentiation 137; CTLA-4 = cytotoxic T-lymphocyte antigen-4; GITR = glucocorticoid-induced tumour necrosis factor receptor; HVEM = herpes virus entry mediator; OX40 = tumour necrosis factor receptor superfamily, member 4; LAG3 = lymphocyte-activation gene 3; PD-1 = programmed death-1; TIM3 = T-cell immunoglobulin and mucin-domain containing-3; VISTA = V-domain immunoglobulin suppressor of T-cell activation.

Source: Mellman et al.[5]

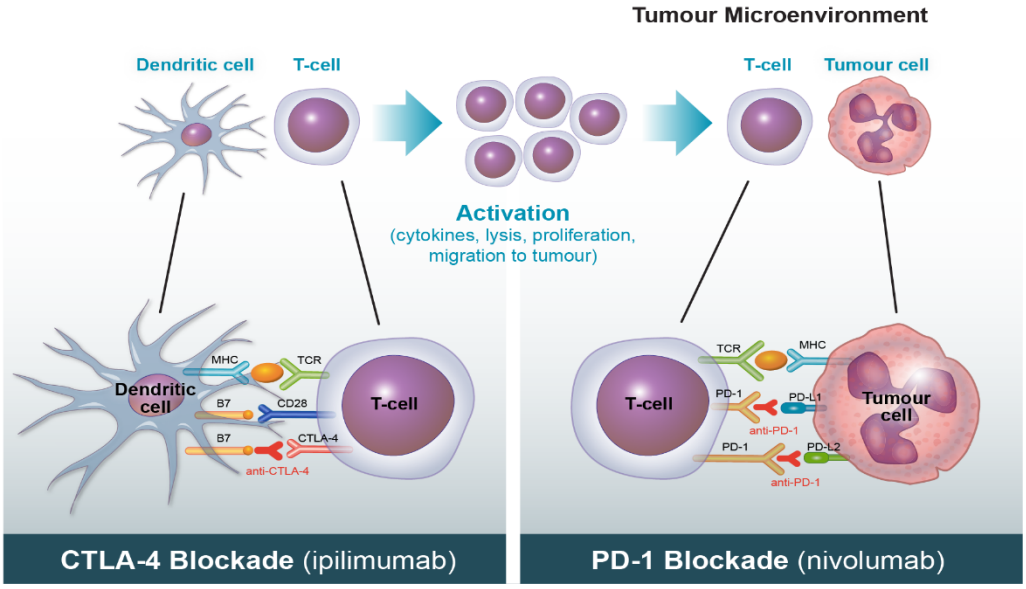
Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with programmed death-ligand 1 (PD-L1) and PD-L2. The PD-1 checkpoint is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed on antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation. Nivolumab potentiates T-cell responses, including antitumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[5,6]

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumour-infiltrating T-effector cells. Inhibition of CTLA-4 signalling can also reduce T-cell regulatory function, which may contribute to a general increase in T-cell responsiveness, including the antitumour immune response.[5,6]

The mechanisms of action of ipilimumab and nivolumab are distinct and complementary, with ipilimumab working early in the immune response by facilitating antigen presentation to naive T-cells in the lymph nodes and nivolumab working later in the immune response on the tumour-specific effector T-cells.[15] Therefore, the combination of nivolumab + ipilimumab potentiates immune-mediated tumour destruction, stimulating the patient's own immune system to directly fight cancer cells (in the same way that it would any other foreign cell), which results in destruction of the tumour through pre-existing, intrinsic processes (Figure 2).

Figure 2. Nivolumab and ipilimumab: mechanism of action for dual immune checkpoint blockade

Ipilimumab (anti–CTLA-4)	Nivolumab (anti–PD-1)
Induces de novo antitumour T-cell responses[11,13]	Restores antitumour T-cell function[7,8]
Enables adaptation to evolving tumour[13,14] Promotes emergence of memory T-cells[12] Causes compensatory increase in tumour PD-L1[13]	Enhances pre-existing T-cell response[7] Increases cytokine production[10]



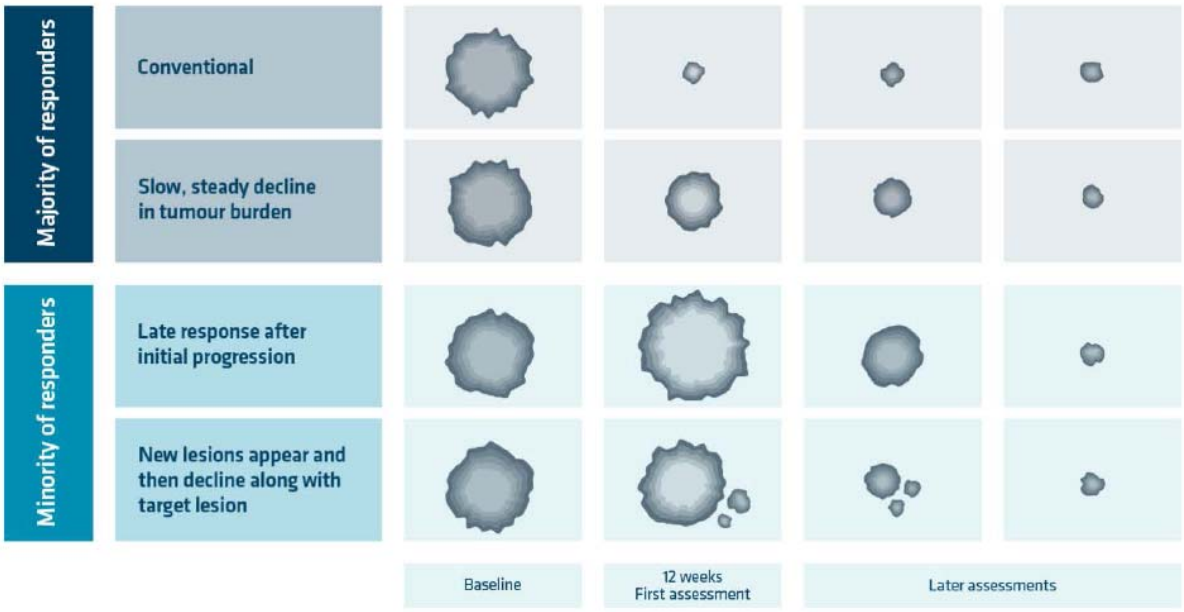
CD28 = cluster of differentiation 28; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; MHC = major histocompatibility complex; PD-1 = programmed death-1; PD-2 = programmed death-2; PD-L1 = programmed death-ligand 1; PD-L2 = programmed death-ligand 2; TCR = T-cell receptor.

Sources: Mellman et al.[5]; Guo et al.[6]

The combined mechanism of action of nivolumab + ipilimumab, which involves the complementary inhibition of CTLA-4 and PD-1, results in increased antitumour activity and may offer the potential of long-term survival to patients with MPM, similar to that observed in other lung cancers.[20,21]

It is important to recognise the key differences between immunotherapies and standard anticancer therapies; these differences arise from the novel mechanisms of action of immunotherapies. First, varying patterns of response can be observed with immunotherapies such that patients who ultimately achieve a positive clinical outcome may have tumours that appear to have enlarged when assessed in the early stages of treatment. This is due to increased T-cell activity that makes the tumour appear larger (pseudoprogression) (Figure 3).[22,23] Second, immunotherapies should not be considered targeted therapies. Although they target specific pathways in the immune system, this is not the same as targeting an abnormal protein resulting from a tumour-specific DNA mutation.

Figure 3. Typical patterns of response observed with immunotherapies



Adapted from Frelaut et al.[23]; Jia et al.[22]

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease background: malignant pleural mesothelioma (MPM)

Mesothelioma is an aggressive cancer arising from mesothelial cells; specialised cells that line serous body cavities and internal organs to provide a protective surface.[24-26] The four main types occur in the linings of the lungs (pleura), abdomen (peritoneum), heart (pericardium), or testicles (tunica vaginalis). MPM is the most common of all mesotheliomas: 80% to 90% of cases are pleural, 15% to 20% are peritoneal, 1% are pericardial, and < 1% are testicular.[27]

Unlike other lung cancers, MPM is a preventable, occupation-related disease: 94% of cases in the UK are caused by prior asbestos exposure while at work, and it is considered an industrial injury.[3,28] MPM is associated with a long latency period of approximately 40 years from asbestos exposure to disease presentation.[29]

B.1.3.1.1 Symptoms, diagnosis, and staging

Presenting symptoms of MPM include shortness of breath, chest pain, cough, sweating, loss of appetite, weight loss, fatigue, and lethargy, all of which severely affect a patient's quality of life (QOL).[30] These symptoms are steadily progressive and cause a high level of distress for both patients and their families.[3]

Diagnosis and screening for MPM is challenging because symptoms can often be non-specific, coupled with the approximate 40-year delayed onset of disease.[31] This means MPM is often diagnosed at an advanced stage: approximately 40% of cases in the 2016-2018 UK National Mesothelioma Audit were diagnosed at stage III/IV, and 35% were unstaged, which may be owing to problems with obtaining sufficient or appropriate biopsy material[32] or because patients are too sick when diagnosed to have a biopsy (clinical expert opinion, Appendix N).

Definitive diagnosis and staging of MPM are done via histological examination of tumour tissue and imaging studies.[31] There are a number of staging classifications for MPM, but all have limitations in routine clinical practice (American Joint Committee on Cancer [AJCC]/National Comprehensive Cancer Network [NCCN]; International Mesothelioma Interest Group [IMIG]).[25] The staging system most often used to describe the growth and spread of pleural mesothelioma in clinical trials is the AJCC TNM (Tumour-Node-Metastasis) staging system. Once the T, N, and M categories have been assigned, this information is combined to define an overall stage (I, II, III, or IV). Patients with disease at a lower stage tend to have a better prognosis[33]:

- Stages I and II usually describe a tumour that has grown into the pleura lining, the chest wall on one side of the chest (stage I) or a tumour that has also invaded the pleura coating the diaphragm, the mediastinum, or the lung (stage II). However, in both cases, the tumour has not spread to the lymph nodes (N0) or to distant sites (M0).
- Stage III mesothelioma is usually a tumour that has loco-regional growth, including the mediastinum, deeper layers of the chest wall, or the surface of the pericardium, with or without involvement of lymph nodes on the same side as the main tumour.

- Stage IV mesothelioma describes a tumour that has spread to other organs in the mediastinum or across the pleura on the other side of the chest, usually with lymph node involvement and sometimes with distant metastasis.

B.1.3.1.2 Histopathology and biomarkers

Mesothelioma can be categorised into three main histological subtypes that affect prognosis: epithelioid, sarcomatoid, and mixed/biphasic; it can also be categorised as a rarer desmoplastic subtype (1%-2% of cases).[34] These subtypes can be broadly classified as epithelioid and non-epithelioid. The epithelioid subtype has the most favourable prognosis (median survival, 13 months), whereas sarcomatoid subtypes have the worst prognosis (median survival, 4 months).[29] British Thoracic Society (BTS) 2018 guidelines recommend that pathologists should report the histological subtype of MPM in all cases.[1] However, the 2016-2018 UK National Mesothelioma Audit showed that a high proportion of cases are not subtyped definitively, with 31% of pathologically confirmed cases classified as unspecified.[32] This likely reflects the difficult nature of biopsy in MPM, as these tumours are heterogeneous in nature, and, in clinical practice, histological subtype can be a broad spectrum that is hard to define (see clinical expert opinion: Appendix N).

B.1.3.1.3 PD-L1 status

MPM tumours have been reported to express PD-L1[35]; however, evidence for the levels of PD-L1 expression in MPM is inconsistent, with wide variation in the threshold cutoffs used and the rates of PD-L1 expression observed in clinical studies (Table 3). As a result, large differences have been reported, with 20% to 70% of specimens tested being considered PD-L1-positive.[36] Unlike other lung cancers in which PD-L1 inhibitors are already approved and PD-L1 testing is standard practice, PD-L1 testing is not routinely performed on biopsies from patients with MPM in the National Health Service (NHS) in England, and the thresholds, scoring methods, and antibodies used to detect PD-L1 expression in MPM are not standardised. Similar to histological subtyping, reliable PD-L1 testing is highly dependent on biopsy, which is technically difficult in MPM because MPM tumours have spatial heterogeneity and the amount of tissue obtained is usually not sufficient for accurate PD-L1 testing. For these reasons and because no PD-L1 inhibitor has shown benefit in MPM, PD-L1 testing is not currently a standard test in the NHS for this patient population (see clinical expert opinion: Appendix N). There is some evidence that PD-L1 expression is associated with poorer survival (Table 3)[35]; however, this may be because non-epithelioid tumours more often express PD-L1.[37] Furthermore, the relationship is unclear owing to limitations described in terms of the inconsistency in testing and definitions means.

Table 3. PD-L1 expression and prognosis in clinical studies with chemotherapy in MPM

Study	No. of patients	Interventions	PD-L1 subgroup		Antibody clone used to detect PD-L1
			Prevalence, n (%)	mOS (months)	
Mansfield et al.[35]	106	Surgery Chemo	**5% cutoff**		5H1-A3
			PD-L1+: 42 (40%)	5	
			PD-L1−: 64 (60%)	14.5	
Cedrés et al.[38]	77	Chemo = 66% No chemo = 26% NR = 8%	**1% cutoff**		E1L3N
			PD-L1+: 16 (21%)	4.8	
			PD-L1−: 61 (79%)	16.3	
Thapa et al.[39]	329	Surgery	**5% cutoff**		E1L3N
			PD-L1+: 100 (32%)	9.8	
			PD-L1−: 181 (58%)	13.5	
			50% cutoff		
			PD-L1+ = 30 (10%)	5.33	
Nguyen et al.[40]	58	BSC = 31 (53%) Chemo = 27 (47%)	**1% cutoff**		SP263
			PD-L1+: 42 (72%)	6	
			PD-L1−: 16 (28%)	15.5	
Sobhani et al.[41]	62	Chemo = 14 (23%) No chemo = 48 (77%) Rad = 4 (6%)	**1% cutoff**		22C3
			PD-L1+: 25 (40%)	12	
			PD-L1−: 37 (60%)	18	
Brosseau et al.[37] (Bio-MAPS cohort)	214/448	PEM/CIS/BEV vs. PEM/CIS	**1% cutoff**		E1L3N (CST/Ozyme)
			PD-L1+: 77 (36%)	12.3	
			PD-L1−: 137 (64%)	22.2	
			50% cutoff		
			PD-L1+: 27 (13%)	10.5	
			PD-L1−: 187 (87%)	19.3	
Scherpereel et al.[42] (MAPS-2)	125	NIVO vs. NIVO + IPI in second-line MPM	**PD-L1−**	NR	28-8 pharmDx
			31 (49%) vs. 27 (44%)		
			1% cutoff		
			PD-L1+: 19 (30%) vs. 22 (35%)		
			25% cutoff		
			PD-L1+: 2 (3%) vs. 5 (8%)		
			50% cutoff		
			PD-L1+: 0 (0%) vs. 3 (5%)		
			Data not available: 13 (21%) vs. 13 (21%)		

Study	No. of patients	Interventions	PD-L1 subgroup		Antibody clone used to detect PD-L1
			Prevalence, n (%)	mOS (months)	
Popat et al.[43] (PROMISE-Meso)	135	PEM vs. gemcitabine or vinorelbine in second-line MPM	**1% cutoff**	NR	SP263
			PD-L1+: 66 (49%)		
			20% cutoff		
			PD-L1+: 25 (19%)		
			Not evaluable		
			6 (4.4%)		

BEV = bevacizumab; BSC = best supportive care; Chemo = chemotherapy; CIS = cisplatin; IPI = ipilimumab; mOS = median overall survival; MPM = malignant pleural mesothelioma; NIVO = nivolumab; NR = not reported; PD-L1 = programmed death-ligand 1; PEM = pembrolizumab; Rad = radiotherapy.

B.1.3.2 Epidemiology of MPM

MPM is a rare lung cancer with a poor prognosis and is considered almost universally fatal.[3]

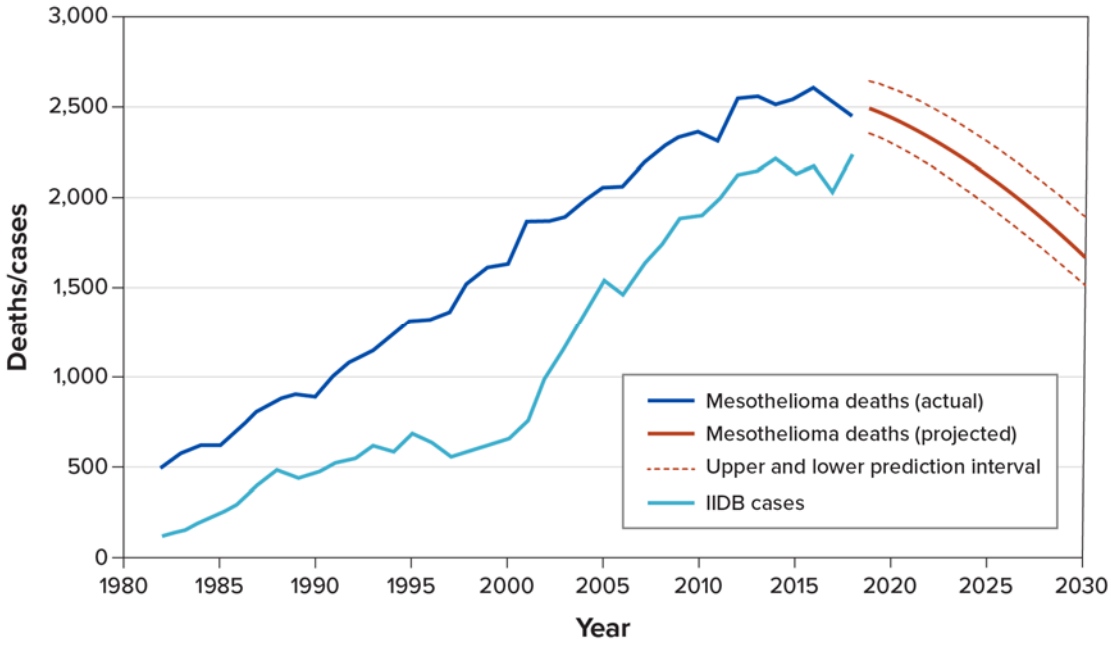
B.1.3.2.1 Incidence, mortality, and risk factors

In the UK in 2017, MPM accounted for < 1% of all new cases of cancer. UK registry data from 2015-2017 show there were 2,727 new cases and 2,490 deaths from mesothelioma per year.[28] The UK National Mesothelioma Audit from 2016-2018 determined an incidence of 6,551 cases of MPM in England over the 3-year study period.[32]

MPM is more common in men than women and in older people owing to the occupational nature and long latency associated with the disease. The 2016-2018 UK audit data show the mean age at diagnosis to be 75.7 years (median age, 76 years), with 83.3% of cases occurring in males.[32] Similar data were observed in a retrospective cohort study of the national Cancer Analysis System (CAS) registry in England, which included all 9,458 patients newly diagnosed with MPM from January 2013 to December 2017. Per baseline characteristics, patients had a median age of 75 years (interquartile range [IQR], 69-81 years), and 83% were male.[44] Owing to the use of asbestos with heavy industry and construction, the incidence rates vary significantly across England, with higher rates in areas of heavy industry (e.g., the northeast and southern England).[3,45]

MPM incidence is related to asbestos exposure over time. Global incidence is estimated to reach its peak in 2020, but in countries where asbestos was only recently eradicated or is still in use, peak incidence is yet to occur.[46] Because the use of asbestos was not banned completely in the UK until 1999,[30] the UK is currently experiencing its peak of expected incident cases (Figure 4),[45] which was confirmed by clinical experts (Appendix N). Rates are expected to fluctuate above and below the predicted peak in years close to the peak. This is due to year-on-year variation in the annual counts, whereas the statistical projection model describes the expected future rates as a smooth curve.[45]

Figure 4. Mesothelioma: observed cases, annual deaths, and projected future deaths to 2030 in Great Britain



IIDB = Industrial Injuries Disablement Benefit.

Source: Health and Safety Executive[45]

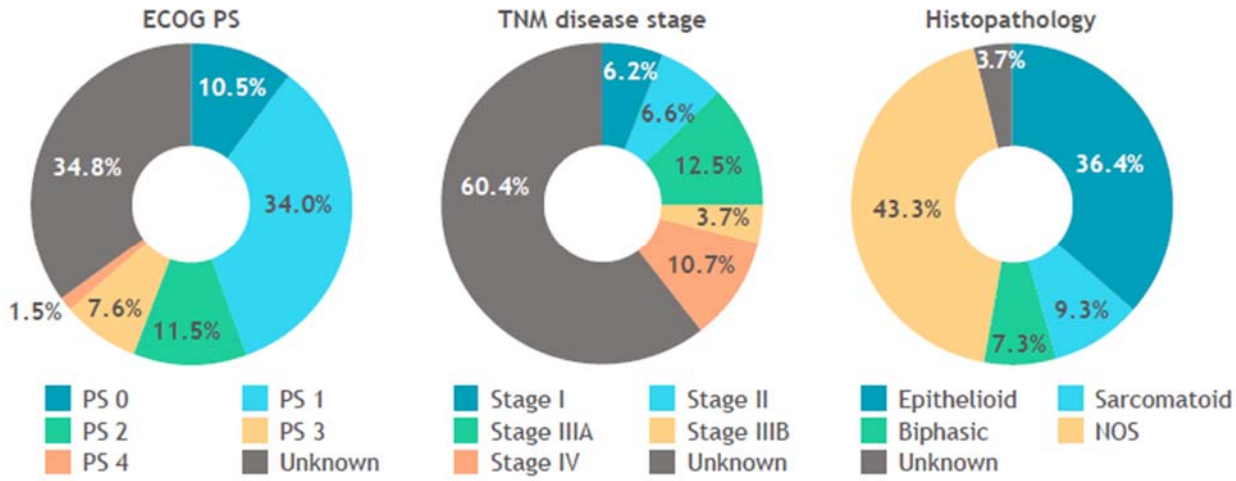
Mortality data from the UK Health and Safety Executive (HSE) show there were 2,446 deaths from mesothelioma (2,050 male, 396 female) in Great Britain in 2018, similar to observed rates in the previous 6 years. Mortality rates up to 2020 are expected to remain at approximately 2,500 per year. More than half of annual deaths occur in those older than 75 years; annual deaths in this age group continue to increase, while deaths in those younger than 70 years are now decreasing.[45]

B.1.3.2.2 Distribution by stage, performance status, and histological subtype

MPM is often diagnosed at a late stage, and patients can be elderly and frail at the time of diagnosis. The 2016-2018 UK National Mesothelioma Audit data show approximately half (51.4%) of patients with MPM have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, and fewer than half were stage I-III at diagnosis (44.9%). However, these data are uncertain because a high proportion of patients had missing status or stage data (19.4% and 34.6%, respectively).[32] Similar data were reported in the CAS registry of patients with MPM in England (N = 9,458), with 35% of patients missing performance status and 60% with missing stage (Figure 5).[44]

For histological subtype, 2016-2018 UK National Mesothelioma Audit data showed that 48% of pathologically confirmed cases were epithelioid, 11% were sarcomatoid, 10% were biphasic/mixed, and 31% were unspecified.[32] Similar data were reported in the CAS registry (Figure 5), with 47% of patients with unknown or unspecified histopathology.[44]

Figure 5. Distribution for ECOG performance status, stage, and histopathology in patients with MPM in the CAS Registry in England, 2013-2017 (N = 9,458)



CAS = Cancer Analysis System; ECOG PS = Eastern Cooperative Oncology Group performance status; MPM = malignant pleural mesothelioma; NOS = not otherwise specified; TNM = Tumour-Node-Metastasis.
Source: Baas et al.[44]

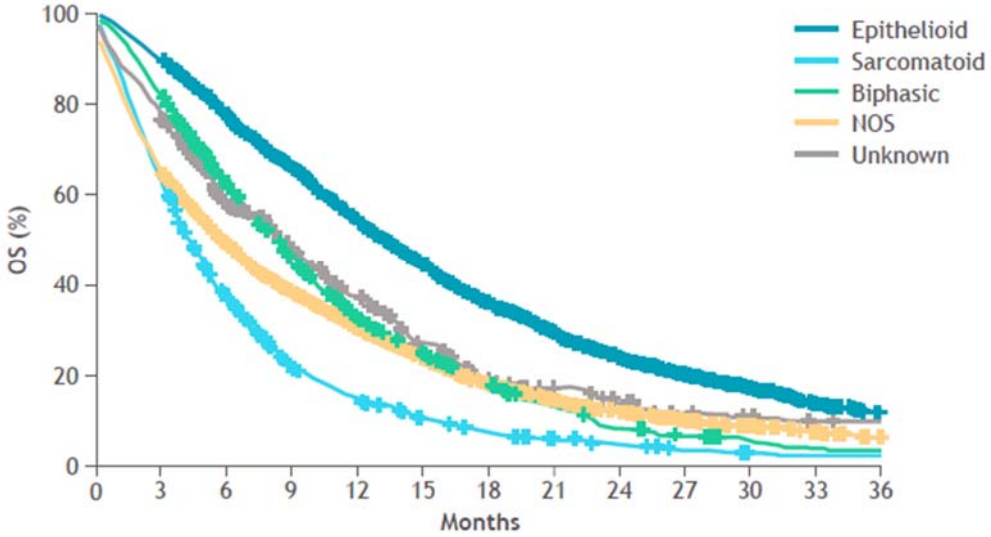
B.1.3.2.3 Survival

The 2016-2018 UK National Mesothelioma Audit showed low rates of survival from disease diagnosis: only 40% of patients with MPM were alive after 1 year and 10% after 3 years across all stages and subtypes.[32] In the CAS registry of patients with MPM in England (N = 9,458), median overall survival (OS) of the entire study population was 8.3 months (IQR, 3.1-17.2 months); 1-year OS was 38% (95% confidence interval [CI], 37%-39%), 2-year OS was 16% (95% CI, 15%-16%), and 3-year OS was 8% (95% CI, 7%-9%).[44]

There are few reliable UK-wide survival statistics for MPM by stage owing to a lack of staging information; however, 1-year survival is highest for stage I (59%) and lowest for stage IV (30%).[28] Registry data from 1990-2017 in the United States (US) show median OS for patients with MPM was 12 months at stage III/IV and 20 months at stage I.[47]

UK survival data by histological subtype (Figure 6) and by initial line of treatment (Figure 7) were collected in the CAS registry. Results showed that OS varied according to histopathology, with a shorter median OS observed in patients with sarcomatoid MPM (4.3 months), MPM not otherwise specified (5.8 months), and biphasic MPM (8.3 months) than in patients with epithelioid MPM (13.3 months). By treatment, patients undergoing surgery + systemic anticancer therapy (SACT) as initial treatment had the longest survival (median OS, 21.5 months); however, only 20% were alive 3 years after diagnosis. Among unresected patients treated with SACT, OS remained poor (median OS, 12.9 months) with only 10% of patients alive 3 years after diagnosis. Survival among patients receiving best supportive care (BSC) was very poor (median OS, 3.8 months).[44]

Figure 6. Unadjusted overall survival from diagnosis by histopathology in patients with MPM in England, 2013-2017 (N = 9,458)



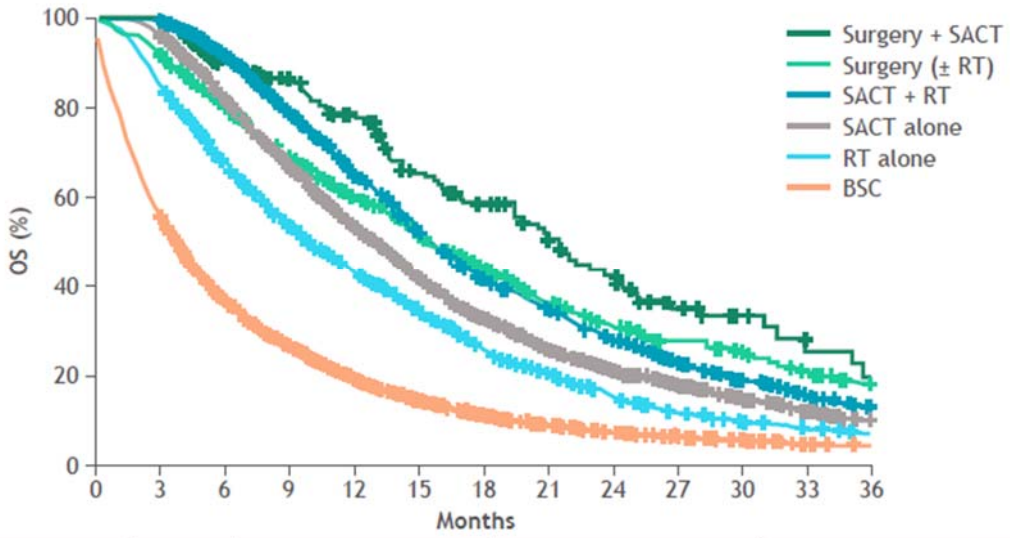
	N	Median OS months (Q1-Q3)	1-year OS		3-year OS	
			n	% (95% CI)	n	% (95% CI)
Epithelioid	3439	13.3 (6.5-23.4)	1588	54 (53-56)	170	12 (11-14)
Sarcomatoid	883	4.3 (2.0-8.2)	111	15 (12-17)	9	2 (1-4)
Biphasic	693	8.3 (4.0-14.7)	189	32 (29-36)	10	3 (1-5)
NOS	4093	5.8 (1.9-14.4)	1102	30 (29-32)	142	6 (6-7)
Unknown	349	8.8 (3.5-16.2)	96	37 (32-43)	7	10 (6-16)

CI = confidence interval. MPM = malignant pleural mesothelioma; NOS = not otherwise specified; OS = overall survival.

Note: One patient was not included because of incomplete data.

Source: Baas et al.[44]

Figure 7. Unadjusted overall survival from diagnosis by initial treatment in patients with MPM in England, 2013-2017 (N = 9,458)



	N	Median OS months (Q1-Q3)	1-year OS		3-year OS	
			n	% (95% CI)	n	% (95% CI)
Surgery + SACT	135	21.5 (13.1-35.1)	84	79 (72-86)	7	20 (11-34)
Surgery (± RT)	478	15.4 (7.4-30.3)	250	60 (55-64)	42	19 (15-23)
SACT + RT	1099	15.7 (10.0-25.9)	663	65 (62-68)	84	13 (11-16)
SACT alone	2059	12.9 (7.3-21.4)	918	53 (51-56)	85	10 (9-12)
RT alone	1077	10.0 (4.8-18.3)	425	44 (41-47)	43	7 (6-9)
BSC	4604	3.8 (1.4-9.6)	742	20 (18-21)	76	5 (4-5)

BSC = best supportive care; CI = confidence interval; MPM = malignant pleural mesothelioma; OS = overall survival; RT = radiotherapy; SACT = systemic anticancer therapy.

Note: One patient was not included because of incomplete data.

Source: Baas et al.[44]

B.1.3.3 Burden of MPM

B.1.3.3.1 Impact on health-related quality of life

Although premature death is the main contribution to the total health loss due to MPM, health-related quality of life (HRQOL) is also severely limited in patients with MPM and their caregivers experience reduced QOL from the time of diagnosis.[48] At presentation, most patients have advanced disease and experience a high symptom burden, with persistent chest pain, dyspnoea, and cough that results in reduced physical activity.[49] In addition, standard of care (SOC) chemotherapy is associated with side effects of nausea and vomiting, sore mouth, and alopecia.[50,51]

Awareness of the incurable, yet preventable nature of MPM leaves many patients in severe emotional distress.[29] Depression and anxiety have been reported more frequently in patients with MPM than in those with other cancers.[29,52] Severe depression and anxiety have been observed in up to half of patients with MPM in the first 3 months after diagnosis.[53,54] Long legal procedures, compensation claims, and other non-clinical issues related to workplace exposure to asbestos add to the burden of MPM and loss of QOL for caregivers.[55]

UK utility data show that treatment-naive patients with MPM experience a significant utility decrement versus population norms, reporting a mean EQ-5D score of 0.69 (range,

−0.60 to 1.00) and mean European Organisation for Research and Treatment Quality of Life Questionnaire–Core Module of Cancer Patients (EORTC QLQ-C30) score of 65 (range, 0-100).[50] Dimensions of HRQOL most affected by MPM diagnosis were Role Functioning and Emotional Well-being, with mean EORTC QLQ-C30 scores of 62 and 79, respectively.[50,51]

Evidence demonstrating the impact of chemotherapy on the HRQOL of patients with MPM is limited. Studies report an improvement in disease-specific symptoms in patients treated with platinum-based doublet chemotherapy (PDC) versus cisplatin alone[51,56] or versus an untreated cohort at baseline.[54] However, improved symptoms were offset by the toxicity associated with chemotherapy, as no study has shown a statistically or clinically meaningful improvement in overall HRQOL for patients treated with PDC relative to active symptom control or cisplatin.[51,57,58]

B.1.3.3.2 Economic burden

Despite its small contribution to the overall cost of health care for lung cancer, the annual per-patient cost for MPM is similar to other lung cancers and poses a substantial burden on health care systems. A US database study showed that 52% of patients visited the emergency department, 78% were hospitalised, and 21% received hospice care only 90 days from diagnosis of advanced MPM.[59] Recent UK cost data are lacking; a Scottish database study in 2000 determined mean hospital costs of £94,204 per patient (£3,507 for day-case and £90,697 for inpatient costs), with a mean of 339 days of hospital treatment per patient from diagnosis until death.[60]

B.1.3.4 Treatment pathway

The goals of treatment for MPM are to prolong survival, reduce tumour size, improve symptoms, and maintain QOL for as long as possible, while minimising the side effects of therapy. Current treatments for MPM are limited to chemotherapy and radiation; for patients with resectable MPM, surgery is also an option.[24,25,61]

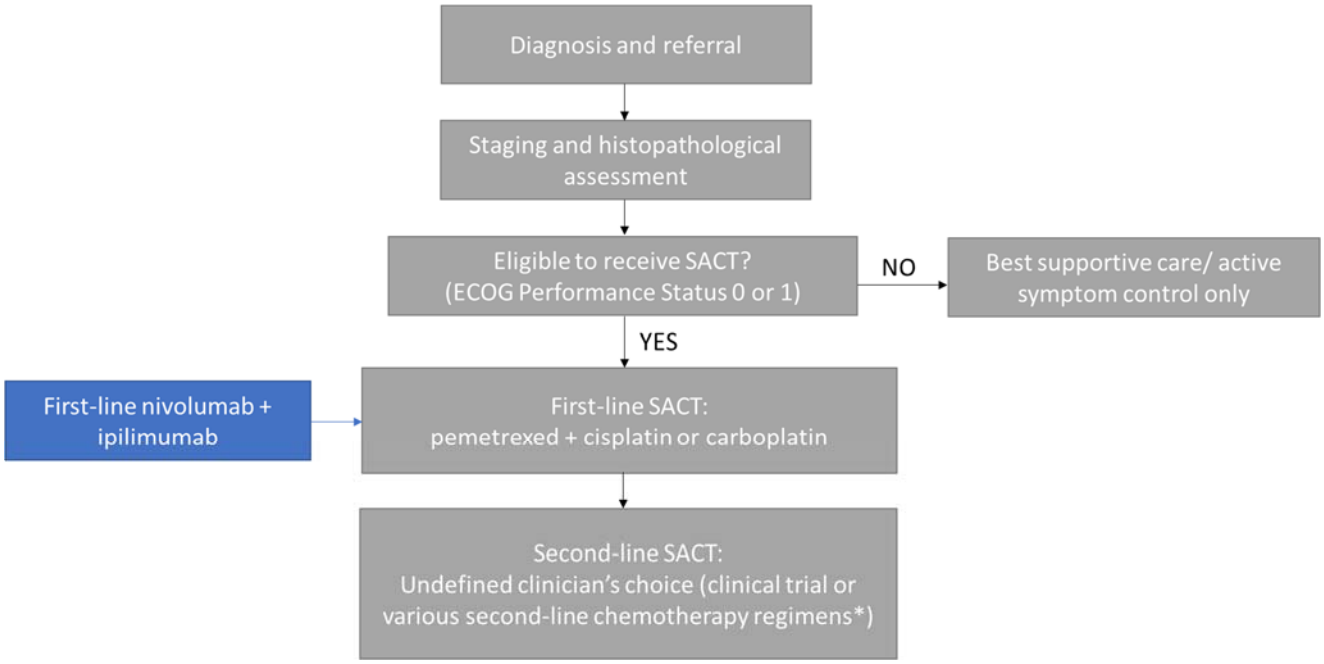
Currently, the first-line SOC SACT for patients with untreated unresectable MPM is PDC, which lacks a strong survival benefit and is poorly tolerated. The only chemotherapy approved for the first-line treatment of MPM is a PDC regimen of pemetrexed in combination with cisplatin, administered intravenously every 3 weeks.[62] NICE TA135 recommends pemetrexed in combination with cisplatin as a treatment option for MPM in people who have a performance status of 0 or 1, are considered to have advanced disease, and for whom surgical resection is considered inappropriate.[2] However, as patients with MPM are often older at diagnosis, they can be too frail to receive SACT or travel for treatment; therefore, not all patients are eligible for chemotherapy. 2016-2018 UK National Mesothelioma Audit data show only 40% of patients received chemotherapy.[32]

Clinical practice guidelines highlight the limited treatment options available in the UK for patients with MPM who are eligible for first-line systemic therapy. The BTS 2018[1] and the European Society for Medical Oncology 2015 guidelines for MPM[63] both recommend PDC for first-line therapy as the only approved SOC, using pemetrexed in combination with cisplatin. The BTS guidelines state that pemetrexed can be replaced with raltitrexed and cisplatin can be replaced with carboplatin as alternatives; however, in clinical practice, raltitrexed is not used in the UK NHS (see Section B.1.3.4.1 and Appendix N).[1] Second-line treatment options

are not well defined because there is no second-line therapy approved for use, and therapies undergoing clinical trials are recommended above any other option.[1] During the COVID-19 pandemic, there is the option to give nivolumab monotherapy instead of second-line chemotherapy to reduce the risk of immunosuppression.[64] Second-line trials with novel agents are ongoing in the UK, such as the Vinorelbine in Mesothelioma (VIM) trial with vinorelbine[65]; however, treatment durations for second-line therapies are brief, and survival is poor.

Nivolumab in combination with ipilimumab is positioned as a first-in-class innovative immunotherapy for the treatment of adults with untreated unresectable MPM. Adoption of nivolumab + ipilimumab would replace current first-line PDC regimens (pemetrexed + cisplatin or carboplatin) to become the new first-line SOC therapy (Figure 8).

Figure 8. Nivolumab + ipilimumab: proposed place in treatment pathway for untreated unresectable MPM



ECOG = Eastern Cooperative Oncology Group; MPM = malignant pleural mesothelioma; SACT = systemic anticancer therapy.

*During the COVID-19 pandemic, there is the option to give nivolumab monotherapy instead of second-line chemotherapy to reduce the risk of immunosuppression.[64]

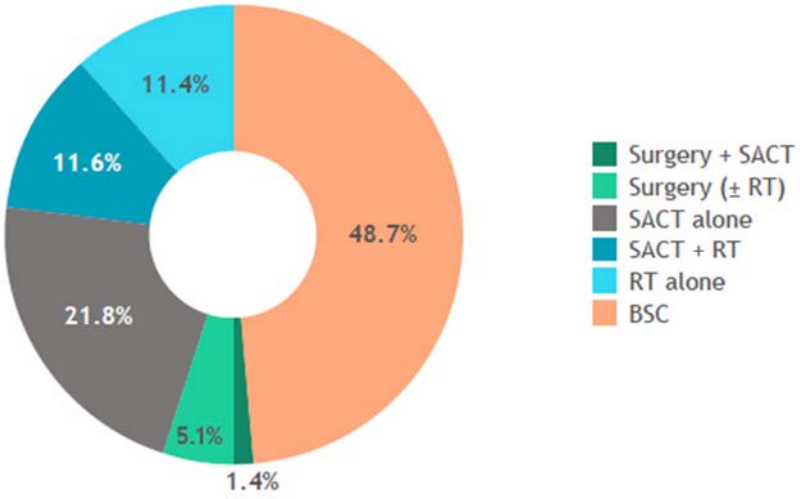
Adapted from NICE[2]; Woolhouse et al.[1]; NICE/NHS England[64]

B.1.3.4.1 Treatment patterns

Real-world treatment patterns in the NHS in England were reported in the 2016-2018 UK National Mesothelioma Audit.[32] Results showed 40% of all patients with MPM in England received chemotherapy from 2016-2018, and 58% of patients with a performance status of 0-1 received chemotherapy. Of the patients who received chemotherapy, pemetrexed with carboplatin was the most common regimen used (48%), followed by pemetrexed with cisplatin (20%), 25% of patients went on to receive more than one line of treatment. A retrospective analysis of the 2013-2017 CAS registry showed similar treatment patterns, with a high proportion of patients with MPM receiving BSC alone or radiotherapy alone (60.1%) (Figure 9).[44] Of unresected patients (n = 8,840), 35.7% received a first-line SACT regimen. Of the patients with follow-up data (n = 3,159), 90.2% received SOC (PDC) and 4.8% received a

clinical trial drug; the proportion of patients receiving SOC was similar across histopathologies. Among patients receiving first-line SACT, 784 (25.2%) received a second-line therapy during the study period; of these, 43.6% received PDC, 18.6% received treatment in a clinical trial, and 24.1% received vinorelbine.

Figure 9. Initial treatment received by patients with MPM in England, 2013-2017 (N = 9,458)



BSC = best supportive care; MPM = malignant pleural mesothelioma; SACT = systemic anticancer therapy; RT = radiotherapy.

Note: Categories not shown because of insufficient patient numbers include surgery + RT + SACT (n < 6) and unknown treatment (n < 6). Adjuvant SACT was defined as SACT received ≤ 60 days after surgery; therefore, some patients may be misclassified as undergoing surgery (± RT) if adjuvant SACT was received > 60 days after surgery.

Source: Baas et al.[44]

UK clinical experts and the BTS report that the NHS standard in clinical practice is pemetrexed + carboplatin. Cisplatin is not given as frequently due to length of chair-time required in the chemotherapy day unit and for logistical reasons, with carboplatin given instead based on an assumption that the two are equally efficacious. Experts state that raltitrexed is not used in the first-line setting within the UK, as there is not a defined subgroup of patients and it is unlicensed (Appendix N and NICE ID1609 response to consultation comments).

Evidence from clinical trials shows first-line treatment of patients with MPM with combination PDC regimens has a limited survival benefit, with a median OS of 12 to 18 months (Table 4). Safety data also show PDC is not well tolerated, with common adverse events (AEs) experienced with both components (Table 5).

Table 4. Summary of efficacy data of PDC for first-line treatment of MPM

PDC-based therapy	Response, %	Median OS, months	1-Year survival, %
Cisplatin + pemetrexed[66]	41.3	12.1	50.3
Tumour-treating field + cisplatin + pemetrexed or carboplatin + pemetrexed[67]	57.0	18.2	62.2
Carboplatin + pemetrexed[68-70]	18.6-25.0	12.7-14.0	51.6-64.0

MPM = malignant pleural mesothelioma; OS = overall survival; PDC = platinum-based doublet chemotherapy.

Table 5. Summary of adverse reactions associated with PDC for first-line treatment of MPM

	Platinum-based agents (cisplatin and carboplatin[a,b])	Pemetrexed[c]
Most common adverse reactions	• **Cisplatin:** haematological (leukopenia, thrombocytopenia, and anaemia), gastrointestinal (anorexia, nausea, vomiting, and diarrhoea), ear disorders (hearing impairment), renal disorders (renal failure, nephrotoxicity, and hyperuricemia), and fever[71] • **Carboplatin:** haematological (neutropenia, leukopenia, thrombocytopenia, and anaemia), gastrointestinal (nausea, vomiting, and abdominal pain) and abnormal blood investigations[72]	Bone marrow suppression (anaemia, neutropenia, leukopenia, thrombocytopenia) and gastrointestinal toxicities (anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis, mucositis, and stomatitis)[62]
Warnings	• **Cisplatin:** renal toxicity, nausea and vomiting, ototoxicity, myelosuppression, and anaphylactic reactions[71] • **Carboplatin:** myelosuppression, allergic reactions; and renal toxicity[72]	None

MPM = malignant pleural mesothelioma; PDC = platinum-based doublet chemotherapy.

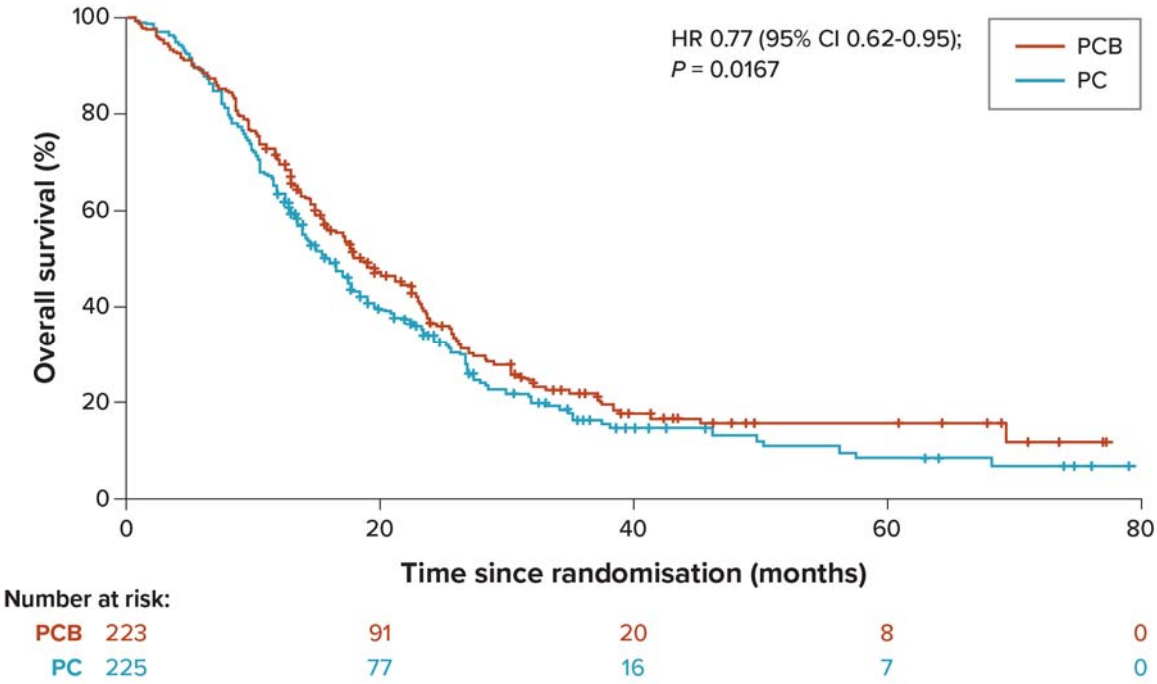
[a] Occurring in ≥ 10% of patients receiving cisplatin.

[b] Occurring in ≥ 10% of patients receiving carboplatin.

[c] Occurring in ≥ 10% of patients treated with pemetrexed used as monotherapy or in combination.

Bevacizumab is not licensed in the UK for the treatment of MPM.[1] However, the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) has reported long-term OS data for patients with untreated unresectable MPM who were treated with chemotherapy: patients were treated with bevacizumab in combination with PDC or with PDC alone (Figure 10).[73] The MAPS trial had a long median follow-up of 39.4 months (IQR, 25.5-54.8 months) and median OS was 18.8 months (95% CI, 15.9-22.6 months) with bevacizumab + PDC and 16.1 months (95% CI, 14.0-17.9 months) with PDC alone. Further discussion on the pattern of long-term survival data in patients with MPM treated with first-line therapy is discussed in Section B.3.3.1.

Figure 10. MAPS trial: overall survival in MPM with first-line PDC with or without bevacizumab



MAPS = Mesothelioma Avastin Cisplatin Pemetrexed Study; MPM = malignant pleural mesothelioma; PCB = pemetrexed + cisplatin + bevacizumab; PC = pemetrexed + cisplatin; PDC = platinum-based doublet chemotherapy.

Source: Zalcman et al.[73]

B.1.3.5 Unmet clinical need

Patients with MPM have a poor prognosis with current treatments, with low 3-year survival rates of approximately 10% across all disease stages and histological subtypes, as described in Section B.1.3.2.[32] The only systemic anticancer therapies approved for use for the treatment of first-line MPM are standard combination PDC regimens, which lack a strong survival benefit, and their cytotoxicity is associated with high rates of AEs. There is a high unmet clinical need for all patients with MPM, regardless of histological subtype or level of PD-L1 expression.

Patients with MPM are often elderly and frail, which means up to 60% of patients are not eligible to receive SACT,[32] so the only treatment available to them is palliative BSC or active symptom control.

There is a high and time-sensitive unmet need in this patient population for a new, innovative treatment to improve survival, as the UK is currently at the peak incidence for MPM (see clinical expert opinion, Appendix N). There are no innovative immunotherapies approved for use in MPM, and no new drug has been licensed in MPM since 2009 (see Innovation, Section B.2.12).[24]

B.1.4 Equality considerations

MPM is a preventable, occupational-related disease caused by asbestos exposure. MPM incidence rates vary across England, with higher rates in areas of heavy industry (e.g., the northeast and southern England). Patients with MPM are often old and diagnosed at a late stage of the disease. Consequently, they can be too frail to travel for treatment, which may limit their treatment options.

B.2 Clinical effectiveness

SUMMARY OF CLINICAL EFFECTIVENESS

CheckMate-743

- CheckMate-743 is the first positive randomised controlled trial (RCT) of any immunotherapy for the first-line treatment of patients with unresectable MPM. A prespecified interim analysis of efficacy data with a minimum follow-up of 22.1 months showed a highly significant OS benefit, increased duration of response and improvements in patient's HRQOL with nivolumab + ipilimumab versus PDC.[18,19]
  - Nivolumab + ipilimumab demonstrated a statistically and clinically significant improvement in OS versus PDC (hazard ratio [HR], 0.74; 96.6% CI, 0.60-0.91; stratified log-rank test, *P* = 0.0020). Median OS was 18.07 months (95% CI, 16.82-21.45 months) and 14.09 months (95% CI, 12.45-16.23 months) for nivolumab + ipilimumab and PDC, respectively. The 24-month OS rate was 40.8% versus 27.0% for nivolumab + ipilimumab versus PDC.
  - Nivolumab + ipilimumab resulted in more durable responses (median duration of response, 11.01 vs. 6.67 months) and more complete responses (CRs) than PDC (5 vs. 0).
  - First-line nivolumab + ipilimumab resulted in improvements in HRQOL versus PDC, as measured by the EQ-5D-3L Utility Index, EQ-5D-3L visual analogue scale (VAS), and Lung Cancer Symptom Scale–Mesothelioma (LCSS-Meso) scales.
- Safety data for nivolumab + ipilimumab in CheckMate-743 show that this dosing and schedule is tolerable in MPM, with an acceptable discontinuation rate due to AEs. The safety profile of nivolumab + ipilimumab in first-line MPM in CheckMate-743 was similar to the known safety profile of the combination in other approved indications and no new safety signals were observed.[18,19]
  - Overall rates of treatment-related grade 3-4 AEs were similar between treatment arms; however, nivolumab + ipilimumab was associated with substantially lower rates of AEs typically associated with chemotherapy when compared with PDC, such as nausea, anaemia, and neutropenia.
- CheckMate-743 is ongoing; updated analyses with additional follow-up will further demonstrate the long-term, durable benefit anticipated with dual immunotherapy with nivolumab + ipilimumab versus PDC. Additional maturity of OS data would reduce current uncertainty on the long-term survival benefit; thus, a period in the Cancer Drugs Fund (CDF) may be beneficial.

B.2.1 Identification and selection of relevant studies

A clinical systematic literature review (SLR) was performed in October 2020 according to NICE requirements to identify studies relevant to nivolumab + ipilimumab for untreated unresectable MPM. Once relevant studies were identified, study characteristics, efficacy, HRQOL, and safety data were extracted, and methodologies were critically appraised according to NICE requirements. See Appendix D for the full search strategy and details of the process and methods used to identify and select the clinical evidence relevant to the submission.

The clinical SLR identified one study for nivolumab + ipilimumab that was relevant to the NICE decision problem: CheckMate-743[18,19] (see Section B.2.2).

B.2.2 List of relevant clinical effectiveness evidence

The clinical effectiveness evidence for nivolumab + ipilimumab from the one study identified as relevant to the NICE decision problem and included in the economic model is summarised below and in Table 6. CheckMate-743 is ongoing, and future analyses will provide long-term efficacy and safety evidence for nivolumab + ipilimumab in MPM.

CheckMate-743 (CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 743, NCT02899299, Study CA209743) is the pivotal phase 3 RCT that compares nivolumab + ipilimumab versus standard PDC (pemetrexed + cisplatin or carboplatin) in adults with untreated unresectable MPM. A prespecified interim analysis of 419 observed events (89% of events required for the final OS analysis) with a median follow-up of 29.7 months was presented at the 2020 World Congress on Lung Cancer[18] and published in The Lancet.[19] A final analysis will be performed when 473 deaths have occurred, and data will be submitted for publication.

Table 6. Clinical effectiveness evidence for nivolumab + ipilimumab in untreated unresectable MPM

Study	**CheckMate-743 (NCT02899299)[18,19,74]**			
Study design	Phase 3 multicentre, randomised, open-label, active-controlled trial with 2 groups randomly assigned (1:1), stratified by histology (epithelioid vs. non-epithelioid) and gender.			
Population	Adults with untreated unresectable MPM with an ECOG performance status of 0-1.			
Intervention(s)	Nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W for up to 2 years, n = 303			
Comparator(s)	Cisplatin or carboplatin + pemetrexed Q3W for 6 cycles, n = 302			
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes X
	No			No
Rationale for use/non-use in the model	This is the pivotal trial for nivolumab + ipilimumab using the licensed dose and indicated patient population. Efficacy and safety results were used in the model.			
Reported outcomes specified in the decision problem (bold indicates included in model)	Primary endpoint: **OS** Secondary endpoints**: PFS by BICR**, ORR Exploratory endpoints: **AEs, HRQOL (EQ-5D-3L)**			
All other reported outcomes	Secondary endpoints: DCR, composite correlation of PD-L1 and efficacy (ORR, PFS, OS)			

AE = adverse event; BICR = blinded independent central review; DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; MPM = malignant pleural mesothelioma; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks.

Note: Outcomes in bold are included in the economic model.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 CheckMate-743 methodology

CheckMate-743 is the pivotal phase 3 RCT providing the key efficacy and safety data for nivolumab + ipilimumab included in the economic model. Table 7 presents details of the trial methodology; further details on endpoints and statistical analyses are described in Section B.2.4.

Table 7. CheckMate-743: summary of trial methodology

Location	103 sites in Australia, New Zealand, Europe, Asia, North America, and South America (6 sites in the UK)	
Trial design	International, multicentre, randomised, open-label, active-controlled phase 3 trial	
Eligibility criteria for participants	Inclusion criteria: • Males and females aged ≥ 18 years. • Histological diagnosis of MPM; determination of epithelioid vs. non-epithelioid histology, thoracoscopy is highly recommended. • Must have advanced unresectable disease that is not amenable to therapy with curative intent (surgery with or without chemotherapy). • Available (archival and/or fresh) pathological samples for centralised PD-L1 IHC testing. • Prior palliative radiotherapy is acceptable; however, ≥ 14 days must have passed prior to first treatment, and all signs of toxicity must have remitted. Prior prophylactic radiotherapy to a pleurodesis drainage tract or biopsy site is allowed. • ECOG PS 0-1. • Measurable disease is defined as: – Mesothelioma tumour thickness perpendicular to the chest wall or mediastinum that can be measured in up to 2 positions at 3 separate levels on transverse cuts of computed tomography scan (cuts must be ≥ 10 mm apart), for a total of up to 6 measurements. Each single tumour measurement must be ≥ 10 mm to qualify as measurable disease and contribute to the sum that defines the pleural measurement. – Non-pleural metastatic target lesions measured unidimensionally as per RECIST v1.1 criteria.	Exclusion criteria: • Primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma. • Brain metastasis, except if surgically resected or treated with stereotaxic radiotherapy with no evolution within the 3 months before inclusion. In addition, patients must be asymptomatic and either off corticosteroids or on a stable or decreasing dosage of 10 mg daily prednisone (or equivalent) for ≥ 2 weeks prior to first treatment. • Undetermined histology of epithelioid vs. non-epithelioid status. • Prior treatment with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti–CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways. • Prior therapy for MPM (including chemotherapy [adjuvant, neoadjuvant], radical pleuropneumonectomy with or without intensity-modulated radiotherapy, and non-palliative radiotherapy). • Prior intraoperative or intracavitary chemotherapy for pleural mesothelioma. • Patients with previous malignancies (except non-melanoma skin cancers and in situ cancers such as bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved ≥ 3 years prior to first study period. • Other active malignancy requiring concurrent intervention or where

	– Patients who present without pleural lesions that can be considered measurable but with metastatic lesions meeting criteria for target lesion by RECIST v1.1 criteria may be considered for inclusion after consultation with the Medical Monitor.	concurrent intervention is anticipated while on study. • Patients with an active, known, or suspected autoimmune disease. • Patients with type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (e.g., vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol. • Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first treatment. Inhaled or topical steroids and adrenal replacement steroid > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease. • Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. • Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.
Settings and locations where the data were collected	See location	
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Permitted and disallowed concomitant medication**	• **Nivolumab + ipilimumab (n = 303)**: nivolumab (3 mg/kg Q3W) administered intravenously + ipilimumab (1 mg/kg Q6W) until disease progression, unacceptable toxicity, or a maximum treatment duration of 2 years • **PDC (n = 302)** pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin (AUC of 5 mg/mL/minute), on day 1 of a 21-day cycle for 6 cycles No dose modifications or dose reductions of nivolumab or ipilimumab were allowed. Doses of nivolumab and/or ipilimumab could be interrupted, delayed, or discontinued depending on how well the patient tolerated treatment. Dosing visits were not skipped, only delayed. Patients receiving ipilimumab in combination with nivolumab that had drug-related toxicities that met the criteria for dose delay had both drugs (ipilimumab and nivolumab) delayed until retreatment criteria were met. Cisplatin or carboplatin in combination with pemetrexed was administered according to label and/or local policy in terms of infusion schema (including, but not limited to, hydration protocols). The use of cisplatin was preferred; however, carboplatin could be used at the discretion of the investigator. The choice of cisplatin or carboplatin occurred after randomisation. Switching from cisplatin to carboplatin and vice versa were allowed, and the reason for that switch had to be reported in the case report form. If switching was due to toxicity and either cisplatin or carboplatin was	

	discontinued, the other study drug could be continued for the remainder of the cycles. Dose reductions and delayed doses were permitted for chemotherapy, per protocol. Permitted and disallowed concomitant medications are described in the inclusion and exclusion criteria above.
Primary outcomes (including scoring methods and timings of assessments)	Primary endpoint: OS defined as the time from randomisation to the date of death from any cause. OS was assessed at follow-up visits 1 and 2[a] and then every 3 months thereafter (via visit, phone, or e-mail). A patient who had not died was censored at the date of last contact (or "last known alive date"). OS was censored at the date of randomisation for patients who were randomised but had no follow-up.
Other outcomes used in the economic model/ specified in the scope	Secondary endpoints included PFS, ORR, TTR, DOR, and safety. All time-to-event secondary endpoints were defined as from time of randomisation. Health-related quality of life was an exploratory endpoint, with the EQ-5D-3L and LCSS-Meso collected before each dose of study treatment through 12 weeks on study after the initial dose, then every 6 weeks thereafter for the first 12 months, and every 12 weeks thereafter until progression or study discontinuation.
Preplanned subgroups	The primary efficacy analysis was conducted on the all-comers population, consisting of all patients randomised. Prespecified subgroup analyses also included age, sex, race, ECOG PS, histology, and PD-L1 expression.

AUC = area under the curve; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; IHC = immunohistochemistry; LCSS-Meso = Lung Cancer Symptom Scale–Mesothelioma; MPM = malignant pleural mesothelioma; ORR = objective response rate; OS = overall survival; PD 1 = programmed death-1; PDC = platinum-based doublet chemotherapy; PD-L1 = programmed death-ligand 1; PD-L2 = programmed death-ligand 2; PFS = progression-free survival; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST = Response Evaluation Criteria in Solid Tumours; TTR = time to response; UK = United Kingdom.

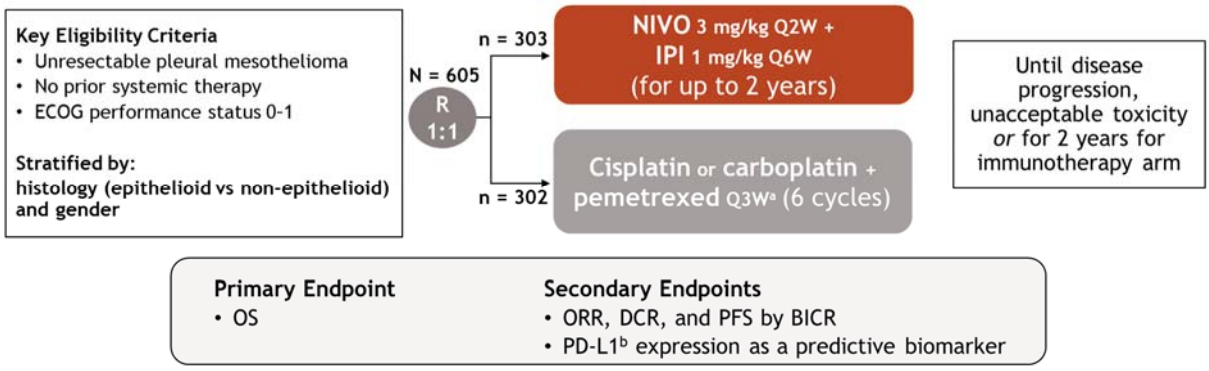
[a] Follow-up visit 1 = 30 days from the last dose ± 7 days or coincides with the date of discontinuation (± 7 days) if date of discontinuation is > 35 days after last dose. Follow-up visit 2 = 90 days (± 7 days) from follow-up visit 1.

Sources: ClinicalTrials.gov[74]; Bristol-Myers Squibb[4]; Bristol-Myers Squibb data on file[75]

B.2.3.2 CheckMate-743: trial design

In CheckMate-743, participants were randomised in a 1:1 ratio to receive either nivolumab + ipilimumab for up to 2 years or PDC for 6 cycles (Figure 11).

Figure 11. CheckMate-743 trial design



AUC = area under the curve; BICR = blinded independent central review; DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; IPI = ipilimumab; NIVO = nivolumab; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks; R = randomisation.

[a] Cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2).

[b] Determined by PD-L1 IHC 28-8 pharmDx assay (Dako).

Source: Baas[18]

B.2.3.2.1 Trial amendments

The original protocol for this study was published in May 2016. There were two global revisions to the amended protocol in April 2019 that included the following two major changes[4]:

- Change of progression-free survival (PFS) from coprimary to secondary endpoint and removal of hierarchical testing of secondary endpoints
- Update of statistical assumption for primary analysis
  - Change in delay in treatment effect assumption from 4 to 6 months in piecewise exponential model for OS in the nivolumab + ipilimumab arm
  - Assumption for median OS in the PDC arm changed from 15 to 16 months

There were two distinct reasons for changing PFS from a primary to secondary endpoint:

- Disease-specific reason: based on 2018 US Food and Drug Administration (FDA) guidance that objective response rate (ORR) and PFS assessments could be imprecise in tumours in which there was a lack of demarcated margins, as in mesothelioma.[76]
- Experience and observation with immunotherapy regimens: PFS and ORR may not adequately characterise the long-term benefit of immunotherapy. There was increased evidence in immunotherapy trials showing that PFS was often not a reliable endpoint to assess clinical benefit, particularly when the comparator was chemotherapy.

The statistical assumptions were modified (changed delayed separation from 4 to 6 months, and median chemotherapy from 15 to 16 months) for the following reasons:

- Data with immunotherapies including nivolumab + ipilimumab versus chemotherapy in non-small cell lung cancer (NSCLC) showing approximately 6 months of delayed separation

- Recently published data of median OS in mesothelioma studies (MAPS and LUME-meso) indicating better survival outcomes for PDC[73,77]

B.2.3.3 CheckMate-743: baseline characteristics

Baseline characteristics in all randomised patients in CheckMate-743 were balanced between treatment arms (Table 8). Overall, the median age of all randomised patients was 69.0 years. Most patients were male (77.2%) and white (85.3%). At study baseline, most patients had advanced disease (stage IV, 51.1%; stage III, 34.5%) and epithelioid tumour histology (75.4%). Overall, 24.6% of patients had non-epithelioid tumour histology, which included tumours with mixed (8.9%), sarcomatoid (11.7%), or other (4.0%) histology.[4]

For PD-L1 expression, 97% of patients were quantifiable at baseline, of whom 77.0% had baseline PD-L1 expression ≥ 1%. As a result, the number of patients in CheckMate-743 who were PD-L1 negative was low, with only 23% with PD-L1 < 1%.[4]

Regions that enrolled patients included Europe (58.2%), Asia (10.7%), and North America (9.8%), and rest of the world (21.3%). CheckMate-743 included 6 UK sites at which 54 patients were enrolled (7.6% of the total enrolled) and 38 patients were randomised (6.3% of the total randomised).[4] UK clinical experts confirmed that the trial population was representative of a treatment-naive MPM population in England (Appendix N).

Patient disposition and flow in CheckMate-743 are described in more detail in Appendix E.

Table 8. CheckMate-743: baseline demographics (all randomised patients)

	Nivolumab + ipilimumab (n = 303)	PDC (n = 302)	Total (N = 605)
Age, median (IQR), years	69 (65-75)	69 (62-75)	69 (64-75)
Male, %	77	77	77
ECOG performance status, %			
0	38	42	40
1	62	57	60
Disease stage at study entry			
I	4	7	5
II	8	7	7
III	34	35	35
IV	53	49	51
Unknown	2	2	2
Smoking status, %			
Never	42	40	41
Current/former	57	57	57
Histology,[a] %			
Epithelioid	76	75	75
Non-epithelioid[b]	24	25	25
Prior radiotherapy, %	10	9	9
PD-L1 quantifiable at baseline,[c] n	289	297	586

	Nivolumab + ipilimumab (n = 303)	PDC (n = 302)	Total (N = 605)
< 1%,[d] %	20	26	23
≥ 1%,[d] %	80	74	77

ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; IQR = interquartile range; PDC = platinum-based doublet chemotherapy; PD-L1 = programmed death-ligand 1.

[a] Based on case report form source.

[b] Included 47% sarcomatoid and 53% mixed/other in the nivolumab + ipilimumab arm and 48% and 52%, respectively, in the chemotherapy arm.

[c] Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako).

[d] Based on PD-L1 quantifiable at baseline, 95% and 98% of patients in the nivolumab + ipilimumab and chemotherapy arms, respectively.

Sources: Baas[18]; Bristol-Myers Squibb[4]; Baas et al.[19]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 CheckMate-743: objectives and endpoints

The primary objective of CheckMate-743 was to compare the OS of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin as first-line treatment in patients with unresectable MPM.[4]

The primary endpoint was OS, which was defined as the time from randomisation to the date of death from any cause. Overall survival was censored at the date of randomisation for patients who were randomised but had no follow-up.

Secondary objectives were to assess the ORR, disease control rate, and PFS as determined by blinded independent central review (BICR) of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin as first-line treatment in patients with unresectable MPM and to evaluate whether PD-L1 expression was a predictive biomarker for ORR, PFS, and OS.[4] Secondary endpoints were defined as follows[4]:

- Objective response rate was defined as the number of randomised patients who achieve a best response of complete response (CR) or partial response (PR) based on BICR assessments (using adapted modified Response Evaluation Criteria in Solid Tumours (mRECIST) and/or RECIST v1.1 criteria) divided by the number of all randomised patients. Best overall response (BOR) was defined as the best response, as determined by the BICR, recorded between the date of randomisation and the date of objectively documented progression per adapted mRECIST and/or RECIST v1.1 criteria or the date of subsequent therapy (including tumour-directed radiotherapy and tumour-directed surgery), whichever occurs first. For patients without documented progression or subsequent therapy, all available response designations contributed to the BOR determination. Confirmation of response was required at least 4 weeks after the initial response. As part of the evaluation of ORR, duration of response (DOR) and time to response were evaluated as follows:
  - Duration of response was defined as the time between the date of first documented response (CR or PR) to the date of the first documented tumour progression as determined by the BICR (per adapted mRECIST and/or RECIST v1.1 criteria) or

death due to any cause, whichever occurs first. Duration of response was evaluated for responders (confirmed CR or PR) only.

  - Time to response was defined as the time from randomisation to the date of the first confirmed documented response (CR or PR), as assessed by the BICR. Time to response was evaluated for responders (confirmed CR or PR) only.

- Disease control rate was defined as the proportion of all randomised patients whose BOR was CR, PR, or stable disease (SD) per adapted mRECIST and/or RECIST v1.1 criteria as assessed by BICR.
- Progression-free survival:
  - The primary definition of PFS (PFS truncated at subsequent therapy) was defined as the time between the date of randomisation and the date of first documented tumour progression, based on BICR assessments (per adapted mRECIST and/or RECIST v1.1 criteria), or death due to any cause, whichever occurs first. Patients who died without a reported progression were considered to have progressed on the date of their death.
  - The secondary definition of PFS (does not account for subsequent therapy) was defined as the time between the date of randomisation and the date of first documented tumour progression, based on BICR assessments (per adapted mRECIST and/or RECIST v1.1 criteria), or death due to any cause, whichever occurs first.
- PD-L1 expression was defined as the percentage of tumour cell membrane staining in a minimum of 100 evaluable tumour cells per validated PD-L1 immunohistochemistry assay (Dako) using 28-8 pharmDX monoclonal antibodies. This was referred to as *quantifiable PD-L1 expression*. If the PD-L1 staining could not be quantified, it was further classified as follows:
  - Indeterminate: Tumour cell membrane staining hampered for reasons attributed to the biology of the tumour tissue sample and not because of improper sample preparation or handling.
  - Not evaluable: Tumour tissue sample was not optimally collected or prepared and PD-L1 expression was neither quantifiable nor indeterminate. Not evaluable can be determined from the haematoxylin and eosin process before the tumour biopsy specimen is sent for PD-L1 evaluation or from the haematoxylin and eosin process during PD-L1 evaluation.
- Patients with missing PD-L1 expression were patients with no tumour tissue sample available for evaluation.

Exploratory objectives were to assess the safety and tolerability of nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin as first-line treatment in patients with unresectable MPM, patient's overall health status and utility, and cancer-related symptoms and QOL. Objectives were defined as follows:

- Safety: The assessment of safety was based on the incidence of AEs, serious AEs (SAEs), AEs leading to discontinuation, AEs leading to dose modification, select AEs for EU submission, immune-mediated AEs (IMAEs) for US submission, other events of special interest, and deaths. The use of immune-modulating concomitant

medication was summarised. In addition, clinical laboratory tests and immunogenicity (i.e., development of antidrug antibody) were analysed.

- EQ-5D-3L: A change from baseline of 0.08 for the Utility Index score and of 7 for the VAS were considered minimally important differences (MIDs) for the EQ-5D-3L.
- LCSS-Meso: Disease-related symptom deterioration rate by week 12 was defined as the proportion of randomised patients who had an increase of ≥ 10 points from baseline in LCSS-Meso Average Symptom Burden Index (ASBI) score at any time between randomisation and week 12.

B.2.4.2 CheckMate-743: statistical analyses and populations analysed

Table 9 provides a summary of the planned statistical analyses in CheckMate-743; Table 10 presents a description of the analysis populations provided in this submission.

Table 9. Summary of the statistical analyses of CheckMate-743

Hypothesis objective	To compare the OS of nivolumab + ipilimumab vs. pemetrexed + cisplatin or carboplatin as first-line treatment in patients with unresectable MPM
Statistical analysis	• OS: compared between the treatment groups at the interim and final analyses using a stratified log-rank test (stratification factors: histology and sex). There was 1 planned interim analysis for superiority of OS at approximately 85% of total events. An O'Brien and Fleming α-spending function was to be used to determine the nominal significance levels for the interim and final analyses. The stratified hazard ratio between the treatment groups was to be presented along with 100*(1-α)% CI (adjusted for interim). In addition, the 2-sided *P* value was to be reported for the analysis of OS. OS was to be estimated using KM techniques. A 2-sided 95% CI for median OS in each treatment group was to be computed via the log-log transformation method. OS rates at fixed time points (e.g., 6 months, depending on the minimum follow-up) were to be presented along with their associated 95% CIs. These estimates were derived from the KM estimate, and corresponding CIs were derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function. The status of patients who are censored in the OS KM analysis was tabulated for each treatment group using the following categories: – On study (on treatment, in follow-up) – Off study (lost to follow-up, withdrawn consent, never treated) The influence of baseline and demographic characteristics on the treatment effect among all randomised patients was also to be explored for specific subgroups, including age, sex, race, ECOG PS, histology, and PD-L1. • Principal analyses of PFS and ORR were based on the BICR evaluation. No formal testing of the secondary objectives was done. Results were descriptive. PFS was estimated using the KM methodology and analysed similarly to OS. Response and disease control rate estimates were presented along with their exact 2-sided 95% CIs by Clopper and Pearson. • DOR was to be estimated using the KM product limit method. CIs for secondary endpoints were at the 2-sided 95% level. • Safety: Descriptive statistics of safety were presented using MedDRA version 22.1 and NCI-CTCAE version 4.0. All on-study AEs, drug-related AEs, SAEs, drug-related SAEs, IMAEs, and select AEs were tabulated using worst grade per NCI-CTCAE version 4.0 criteria by system organ class and preferred term. Frequency, management, and resolution of IMAEs and select AEs were analysed.

	• Patient-reported outcome analyses: Continuous data were described using descriptive statistics. Categorical data were summarised using counts and percentages, for which "missing" was used when applicable. Where relevant, significance testing was 2-sided at the 0.05 level, with no adjustment for multiplicity.
Sample size, power calculation	For the OS primary endpoint, an overall two-sided alpha (type 1 error rate) was set at 0.05. Approximately 600 patients were to be randomised with 1:1 ratio to two treatment arms (actual was 605 randomised). 473 OS events were needed for the final analysis. The sample size was calculated to compare OS between nivolumab + ipilimumab (Arm A) vs. pemetrexed + cisplatin or carboplatin regimen (Arm B). One formal interim analysis was planned for OS at 403 OS events. Key design parameters for the primary analysis were as follows: • Targeted power: 90% • Target hazard ratio: 0.72 – 0-6 months: 1 – 6-34 months: 0.767 – After 34 months: 0.002 • Alpha: 0.05, 2-sided (0.03 at interim; 0.041 at final analyses) • Sample size: 606 • Target number of events: 473 • Expected number of events for interim analysis: 403 (85% of target) • Duration (monthly accrual rate = 34 patients): 56 months
Data management and patient withdrawals	OS was censored on the last date a patient was known to be alive. For PFS, patients who died with no reported progression were considered to have progressed on the date of death. Patients who did not progress or die were censored on the date of their last evaluable tumour assessment. Patients who did not have any on-study tumour assessments and did not die were censored on their date of randomisation. Patients who had palliative local therapy or initiated anticancer therapy without a prior reported progression were censored on the date of their last evaluable tumour assessment on or before the initiation of subsequent anticancer therapy or palliative local therapy. For DOR, patients who did not progress or die were censored on the date of their last evaluable tumour assessment. Patients who started subsequent therapy without a prior reported progression were censored at the last evaluable tumour assessments before initiation of the subsequent anticancer therapy. Patients who died without a reported prior progression were considered to have progressed on the date of their death. For patients who neither progressed nor died, DOR was censored on the date of their last evaluable tumour assessment.
Missing data	If after all attempts, the patient remained lost to follow-up, then the last known alive date as determined by the investigator was reported and documented in the patient's medical records.

AE = adverse event; BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; IMAE = immune-mediated adverse event; KM = Kaplan-Meier; MedDRA = Medical Dictionary for Regulatory Activities; MPM = malignant pleural mesothelioma; NCI-CTCAE = Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; SAE = serious adverse event.

Sources: Bristol-Myers Squibb[4]; Bristol-Myers Squibb data on file[75]

Table 10. Analysis populations in CheckMate-743

Population	Nivolumab + ipilimumab	PDC	Total
Enrolled: All enrolled patients who signed the informed consent form and were registered in interactive web response technologies. This population was used for pretreatment disposition.	—	—	713
Randomised: All patients who were randomised to either treatment group. This population was used for demography, protocol deviations, baseline characteristics, and efficacy.	303	302	605
Treated: All randomised patients who received at least 1 dose of study drug. This population was used for drug exposure and safety.	300	284	584
Immunogenicity patients: All treated patients with baseline and at least 1 postbaseline assessment for antidrug antibody. This population was used for analysis of immunogenicity.	269	271	540
All PD-L1–evaluable patients: All PD-L1 tested patients with quantifiable PD-L1 expression.	289	297	586
Patient-reported outcome analysis population: all randomised patients who have either ≥ 1 item completed on the LCSS-Meso or a valid EQ-5D Visual Analogue Scale or EQ-5D-3L Utility Index score at baseline and ≥ 1 matched on-treatment postbaseline assessment.	LCSS-Meso: 258 EQ-5D-3L: 272	LCSS-Meso: 233 EQ-5D-3L: 247	LCSS-Meso: 491 EQ-5D-3L: 519

LCSS-Meso = Lung Cancer Symptom Scale–Mesothelioma; PD-L1 = programmed death-ligand 1.

Sources: Bristol-Myers Squibb[4]; Bristol-Myers Squibb[78]

B.2.4.2.1 Health-related quality of life scoring and minimally important difference definitions

The responder definitions (individual changes) and between-group MIDs for the LCSS-Meso and the EQ-5D-3L are summarised in Table 11.

Table 11. Patient-reported outcome score range, responder definition, and minimally important difference

PRO scale/item	Score range	Individual responder definition threshold (change from baseline)	MID (between groups)
LCSS-Meso symptom subscales: 01 Anorexia (appetite), 02 Fatigue, 03 Cough, 04 Dyspnea, 05 Pain **LCSS-Meso HRQOL items:** 06 Symptom distress, 07 Activity level, 08 Global HRQOL	**Symptoms** 0-100 (0 best score) **Summary (reversed)** 0-100 (100 best score)	10[a]	10[a]
LCSS-Meso ASBI	0-100 (0 best score)	10[a]	10[a]
LCSS-Meso 3IGI	0-300 (300 best score)	30[a]	30[a]

PRO scale/item	Score range	Individual responder definition threshold (change from baseline)	MID (between groups)
EQ-5D VAS	0-100 (100 best score)	7	7[b]
EQ-5D-3L Index Score[c]	−0.59 (UK) to 1 (1 best score)	0.08	0.08[b]

3IGI = 3-Item Global Index; ASBI = Average Symptom Burden Index; HRQOL = health-related quality of life; LCSS-Meso = Lung Cancer Symptom Scale–Mesothelioma; MID = minimally important difference; PRO = patient-reported outcome; UK = United Kingdom; VAS = visual analogue scale.

[a] LCSS-Meso thresholds and MIDs based on Hollen et al.[79] and Sarna et al.[80].

[b] EQ-5D-3L MID from Pickard et al.[81].

[c] UK weights used in this submission.

Source: Bristol-Myers Squibb[78]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Table 12 summarises the quality assessment conducted for CheckMate-743; additional detail is provided in Appendix D.

Table 12. Quality assessment of CheckMate-743 (NCT02899299)

Was randomisation carried out appropriately?	Yes/No
Was the concealment of treatment allocation adequate?	No—open-label trial
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No—open-label trial
Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an ITT analysis? **If so, was this appropriate and were appropriate methods used to account for missing data?**	Yes
Did the authors of the study publication declare any conflicts of interest?	Yes
Does the trial reflect routine clinical practice in England?	Yes

ITT = intention to treat.

Sources: Quality assessment based on NICE[82]; Baas[18]; Baas et al.[19]

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 CheckMate-743

B.2.6.1.1 Summary of clinical effectiveness

Efficacy data presented in this section include results for all patients relevant to NICE's decision problem, which is all randomised patients for CheckMate-743. Subgroup analyses by PD-L1 expression level and histological subtype are presented in Sections B.2.6.1.4 and B.2.6.1.5, with other subgroups presented in Appendix F.

The results presented here are from the interim analysis, based on a database lock 3 April 2020, after 419 observed events with a minimum follow-up of 22.1 months. Most of the patients in both treatment arms received ≥ 90% of planned doses. The median duration of treatment was longer in the nivolumab + ipilimumab arm (5.55 months; IQR, 2.04-11.35 months), than in the PDC arm (3.48 months; IQR, 2.66-3.70). The maximum duration of treatment per protocol was 24 months for nivolumab + ipilimumab and 6 cycles of PDC. A total of 71 patients (23.7%) received more than 12 months of nivolumab + ipilimumab treatment, whereas no patients in the PDC group received treatment for more than 12 months.[18,19]

Table 13 summarises the interim efficacy analyses for CheckMate-743 for all randomised patients; detailed results for each endpoint are described in the sections below.

Table 13. CheckMate-743: efficacy summary, interim analysis: all randomised patients

Outcome	Nivolumab + ipilimumab (n = 303)	PDC (n = 302)
OS		
Median OS (95% CI), months[a]	18.1 (16.8-21.4)	14.1 (12.4-16.2)
HR[b]	0.74	
96.6% CI vs. PDC	0.60-0.91	
95% CI vs. PDC	0.61-0.89	
P value[c]	0.002	
PFS by BICR[a]		
Median PFS (95% CI), months	6.8 (5.6-7.4)	7.2 (6.9-8.0)
HR[b] (95% CI) vs. chemotherapy	1.00 (0.82-1.21)	
ORR per BICR[d]		
ORR,[e] % (95% CI)	40 (34-45)	43 (37-49)
Median TTR, months	2.7	2.5
DOR (95% CI), months[a]	11.0 (8.1-16.5)	6.7 (5.3-7.1)
Best overall response, n (%)		
CR	5 (1.7)	0 (0)
PR	115 (38.0)	129 (42.7)
Stable disease	112 (37.0)	125 (41.4)
Progressive disease	55 (18.2)	14 (4.6)
DCR (95% CI), % (CR+PR+SD)	76.6 (71.4-81.2)	85.1 (80.6-88.9)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; HR = hazard ratio; ORR = objective response rate; OS = overall survival; PDC = platinum-based doublet chemotherapy; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; TTR = time to response.

[a] Kaplan-Meier estimates.

[b] Stratified Cox proportional hazard model.

[c] 2-sided *P* values from stratified log-rank test.

[d] Per adapted modified RECIST for pleural mesothelioma lesions and/or RECIST v1.1 for non-pleural lesions.

[e] 95% CI Clopper and Pearson Method.

Sources: Baas[18]; Bristol-Myers Squibb[4]; Baas et al.[19]

B.2.6.1.2 Primary endpoint: overall survival (all randomised patients)

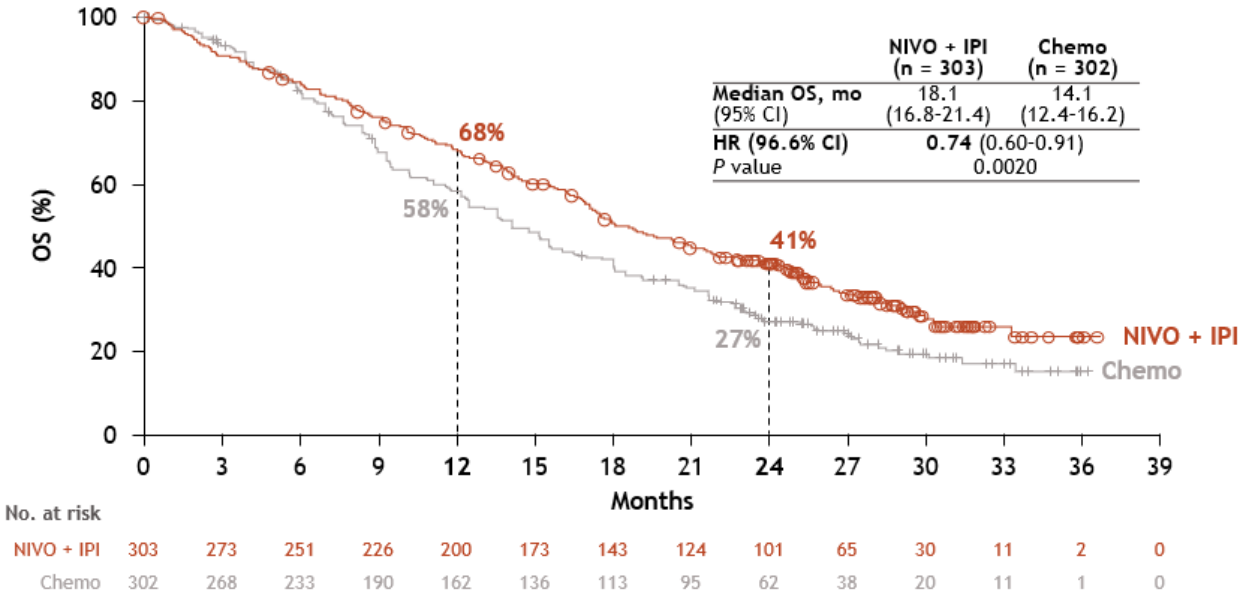
CheckMate-743 met the primary endpoint of OS at the prespecified interim analysis. A statistically significant benefit in terms of OS was seen for patients treated with nivolumab + ipilimumab versus those treated with PDC. Median follow-up for OS was 29.7 months for all randomised patients.[18]

Treatment with nivolumab + ipilimumab reduced the risk of death by 26% when compared with PDC (HR, 0.74; 96.6% CI, 0.60-0.91; stratified log-rank *P* = 0.0020). The median OS was 18.1 months (95% CI, 16.8-21.4 months) for patients treated with nivolumab + ipilimumab versus 14.1 months (95% CI, 12.4-16.2 months) for those treated with PDC, equating to a 4-month survival benefit.[18]

As shown in Figure 12, the Kaplan-Meier (KM) estimated OS rates were higher for nivolumab + ipilimumab than PDC at each time point assessed (Table 14). Two-year OS rates were 41% with nivolumab + ipilimumab and 27% with PDC.[18]

Additional follow-up will further demonstrate the long-term, durable benefit anticipated with dual immunotherapy with nivolumab + ipilimumab, which has been observed with other tumour types.[83,84] This will reduce the current uncertainty regarding the proportion of patients treated with immunotherapy who achieve longer-term survival, which is suggested by an emerging plateau observed in the KM OS curve.

Figure 12. CheckMate-743: Kaplan-Meier plot of overall survival (all randomised patients)



CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival.

Notes: Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm and 41% in the chemo arm; subsequent immunotherapy was received by 3% and 20%, and subsequent chemotherapy by 43% and 32%, respectively.

Chemo in figure refers to platinum-based doublet chemotherapy.

Source: Baas[18]

Table 14. CheckMate-743: overall survival rates—all randomised patients

Overall survival rate (95% CI)	Nivolumab + ipilimumab (n = 303)	PDC (n = 302)
6 months	84.0 (79.4-87.7)	82.2 (77.3-86.2)
12 months	67.9 (62.3-72.8)	57.7 (51.7-63.2)
18 months	50.5 (44.7-56.1)	40.6 (34.8-46.3)
24 months	40.8 (35.1-46.5)	27.0 (21.9-32.4)

CI = confidence interval; PDC = platinum-based doublet chemotherapy.

Note: Based on Kaplan-Meier estimates.

Sources: Baas[18]; Bristol-Myers Squibb[4]; Baas et al.[19]

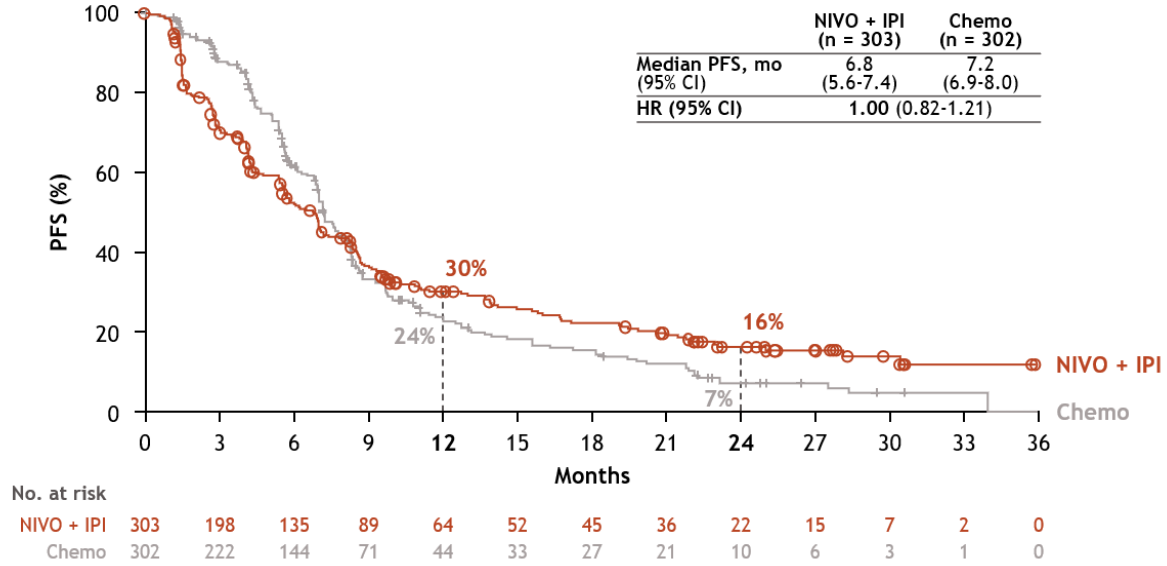
B.2.6.1.3 Secondary endpoints: all randomised patients

Progression-free survival

At the interim analysis, 85.1% of patients in both arms had a PFS event per BICR on or after the last patient last visit date. At the interim analysis, there was no statistically significant difference in PFS in patients treated with nivolumab + ipilimumab compared with PDC. In all randomised patients, median PFS per BICR was 6.77 months (95% CI, 5.59-7.36 months) in the nivolumab + ipilimumab arm and 7.20 months (95% CI, 6.93-8.05 months) in the PDC arm (HR, 1.00; 95% CI, 0.82-1.21). From approximately 8 months, there was sustained separation of the KM curves favouring nivolumab + ipilimumab; this separation was sustained over time,

with an observed plateau with the nivolumab + ipilimumab treatment arm with a proportion of patients who had durable PFS (Figure 13).[18]

Figure 13. CheckMate-743: Kaplan-Meier plot of progression-free survival by blinded independent central review (all randomised patients)



CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PFS = progression-free survival.

Notes: Per adapted mRECIST for pleural mesothelioma lesions and/or RECIST v1.1 for non-pleural lesions.

Chemo in figure refers to platinum-based doublet chemotherapy.

Source: Baas[18]

Although PFS was not significantly different between treatment arms, the KM curves for PFS showed an early advantage for PDC during the initial part of the curve, favouring nivolumab + ipilimumab in the later part of the curve. The plateau of the PFS curve observed in the nivolumab + ipilimumab arm supports the plausibility of a long-term, durable OS benefit for some patients with MPM, which will be confirmed when long-term OS data are available. It is important to note that the evaluation of PFS and ORR in MPM is challenging given the lack of clearly demarcated margins of the lesions leading to wide variability in radiological tumour response determination (as confirmed by clinical experts; see Appendix N).

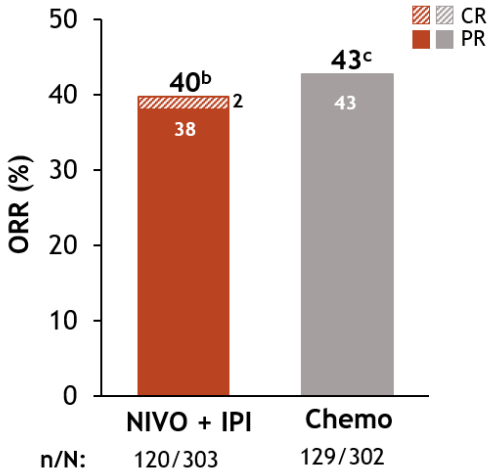
Previous experience from multiple immunotherapy MPM clinical trials has demonstrated that PFS and ORR may not adequately characterise the long-term benefit of immunotherapy treatment. This is commonly observed when immunotherapy alone has been tested against active cytotoxic chemotherapy and likely reflects the mechanisms of action, with chemotherapy providing early but transient disease control and immunotherapy providing a delayed but durable effect. The increase in early PFS events in the nivolumab + ipilimumab arm in CheckMate-743 must be evaluated taking into consideration substantial and likely durable survival benefit thereafter, so OS is the most appropriate outcome for decision making.

Objective response rate

Both the nivolumab + ipilimumab and PDC arms showed similar ORR per BICR. The ORR per BICR was 39.6% (95% CI, 34.1%-45.4%) in the nivolumab + ipilimumab arm and 42.7% (95% CI, 37.1%-48.5%) in the PDC arm (Figure 14).[18] A BOR of CR was observed in

5 patients (1.7%) in the nivolumab + ipilimumab arm compared with no patients in the PDC arm.[4,19]

Figure 14. CheckMate-743: Kaplan-Meier plot of objective response rate per BICR[a] (all randomised patients)



BICR = blinded independent central review; CI = confidence interval; CR = complete response; IPI = ipilimumab; mRECIST = modified Response Evaluation Criteria in Solid Tumours; NIVO = nivolumab; ORR = objective response rate; PR = partial response.

Note: *Chemo* in figure refers to platinum-based doublet chemotherapy.

[a] Per adapted mRECIST for pleural mesothelioma lesions 1 and/or RECIST v1.1 for non-pleural lesions.

[b] 95% CI, 34%-45%.

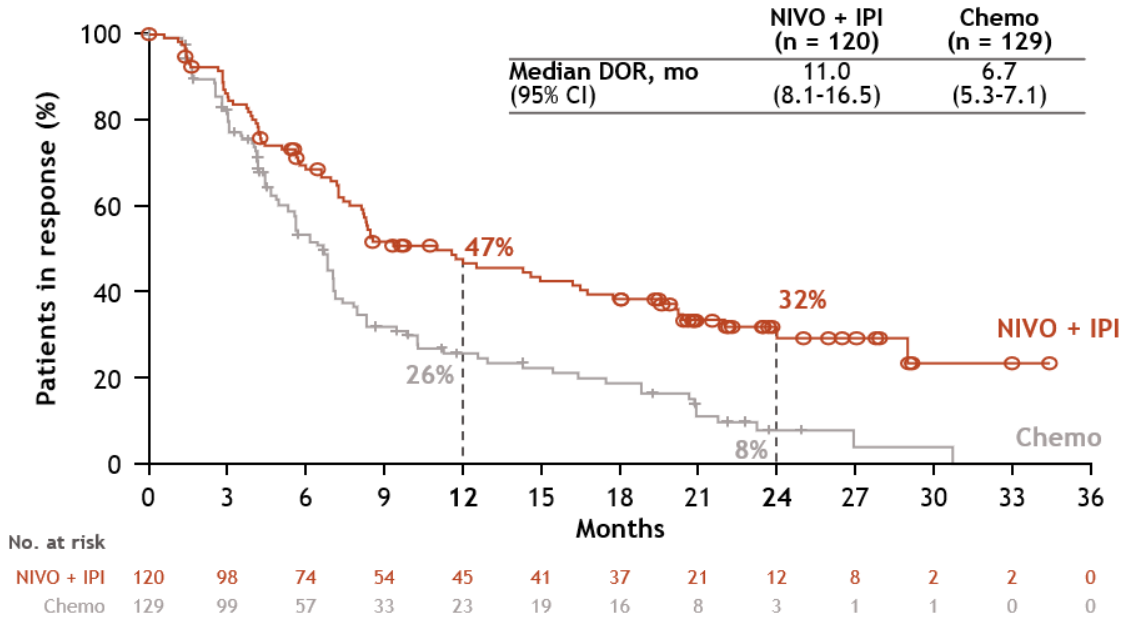
[c] 95% CI, 37%-49%.

Source: Baas[18]

Duration of response

The median DOR was longer for confirmed responders in the nivolumab + ipilimumab arm (11.0 months; 95% CI, 8.1-16.5 months) relative to confirmed responders in the PDC arm (6.7 months; 95% CI, 5.3-7.1 months) (Figure 15). Approximately 47% and 26% of responders in the nivolumab + ipilimumab and PDC arms, respectively, had a DOR of at least 12 months. Separation of the KM curves for DOR occurred at approximately 2 months and favoured nivolumab + ipilimumab over PDC, with an observed plateau in the nivolumab + ipilimumab treatment arm and a proportion of patients who had a durable response.[18] The plateau of the DOR curve observed in the nivolumab + ipilimumab arm supports the plausibility of a long-term, durable OS benefit for some patients with MPM.

Figure 15. CheckMate-743: Kaplan-Meier plot of duration of response per BICR in all responders



BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; IPI = ipilimumab; NIVO = nivolumab.

Note: *Chemo* in figure refers to platinum-based doublet chemotherapy.

Source: Baas[18]

B.2.6.1.4 Secondary endpoint: efficacy by PD-L1 expression

Efficacy according to PD-L1 expression was a secondary endpoint and was explored in the PD-L1–evaluable population, which represented 96.9% of all randomised patients. Additional subgroup data are provided in Section B.2.7 and Appendix F. Table 15 presents a summary of the interim efficacy analyses for CheckMate-743 for all PD-L1–evaluable patients by 1% PD-L1 cutoff; detailed results for each endpoint are described in the sections below.

Table 15. CheckMate-743: efficacy summary, interim analysis—all PD-L1–evaluable patients by 1% PD-L1 cutoff

	PD-L1 < 1% (n = 135)		PD-L1 ≥ 1% (n = 451)	
Outcome	**Nivolumab + ipilimumab (n = 57)**	**PDC (n = 78)**	**Nivolumab + ipilimumab (n = 232)**	**PDC (n = 219)**
OS				
Median OS (95% CI), months[a]	17.3 (10.1-24.3)	16.5 (13.4-20.5)	18.0 (16.8-21.5)	13.3 (11.6-15.4)
HR[b] (95% CI) vs. PDC	0.94 (0.62-1.40)		0.69 (0.55-0.87)	
No. of events	40	58	150	157
PFS by BICR				
Median PFS[a] (95% CI), months	4.1 (2.7-5.6)	8.3 (7.0-11.1)	7.0 (5.8-8.5)	7.1 (6.2-7.6)
HR[b] (95% CI) vs. PDC	1.79 (1.21-2.64)		0.81 (0.64-1.01)	
No. of events	50	53	156	152

Outcome	PD-L1 < 1% (n = 135)		PD-L1 ≥ 1% (n = 451)	
	Nivolumab + ipilimumab (n = 57)	PDC (n = 78)	Nivolumab + ipilimumab (n = 232)	PDC (n = 219)
ORR per BICR				
ORR,[c] % (95% CI)	21.1 (11.4-33.9)	38.5 (27.7-50.2)	43.5 (37.1-50.2)	44.3 (37.6-51.1)
Best overall response, n (%)				
CR	0	0	3 (1.3)	0
PR	12 (21.1)	30 (38.5)	98 (42.2)	97 (44.3)
Stable disease	28 (49.1)	38 (48.7)	79 (34.1)	84 (38.4)
Progressive disease	16 (28.1)	6 (7.7)	37 (15.9)	8 (3.7)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; HR = hazard ratio; ORR = objective response rate; OS = overall survival; PDC = platinum-based doublet chemotherapy; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response.

[a] Kaplan-Meier estimates.

[b] Unstratified Cox proportional hazard model.

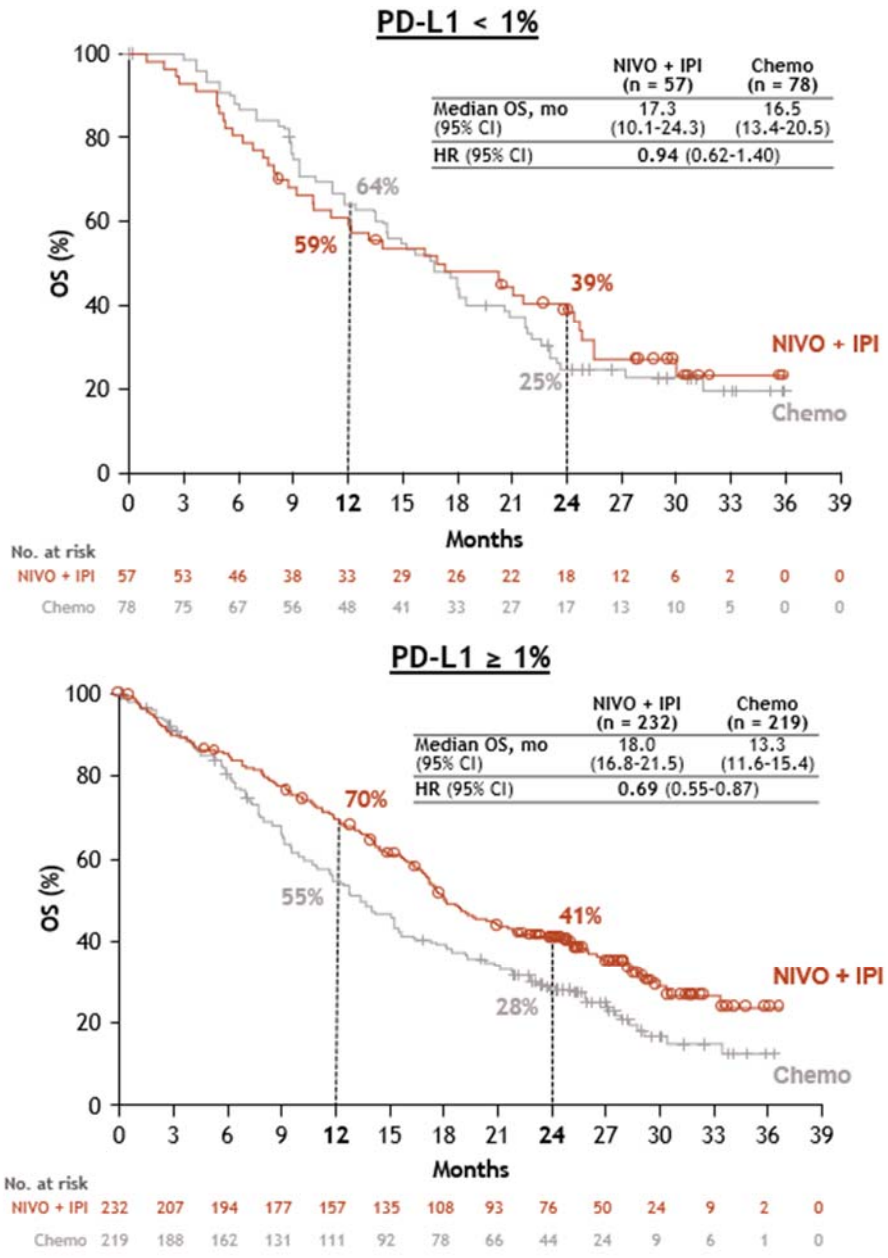
[c] Number of (CR+PR) ÷ number of patients. CI based on the Clopper and Pearson method.

Sources: Baas[18]; Bristol-Myers Squibb[4]

Overall survival by PD-L1 expression

Nivolumab + ipilimumab was associated with better OS versus PDC in both patients with a PD-L1 expression level of ≥ 1% or < 1%. The HRs for PD-L1 < 1% and PD-L1 ≥ 1% subgroups were 0.94 (95% CI, 0.62-1.40) and 0.69 (95% CI, 0.55-0.87), respectively (Figure 16).[18]

Figure 16. CheckMate-743: overall survival by tumour PD-L1 expression



CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PD-L1 = programmed death-ligand 1; OS = overall survival.

Notes: Minimum follow-up, 22.1 months; median follow-up, 29.7 months.

Chemo in figure refers to platinum-based doublet chemotherapy.

Source: Baas[18]

The OS benefit with nivolumab + ipilimumab versus PDC was greater in patients with PD-L1 ≥ 1% than in those with PD-L1 < 1%. However, within treatment groups, a consistent OS benefit was observed with nivolumab + ipilimumab regardless of PD-L1 expression (median OS: PD-L1 < 1%, 17.3 months [95% CI, 10.1-24.3]; PD-L1 ≥ 1%, 18.0 months [95% CI, 16.8-21.5]), while there was unexpected variability in the OS benefit within the PD-L1 subgroups treated with PDC (median OS: PD-L1 < 1%, 16.5 months [95% CI, 13.4-20.5]; PD-L1 ≥ 1%, 13.3 months [95% CI, 11.6-15.4]). The role of PD-L1 as a prognostic marker in

MPM is unclear; therefore, the OS benefit is likely due to the variability in PDC performance and a higher OS in patients with PD-L1–negative tumours treated with PDC, rather than a lower OS in PD-L1–positive tumours in the nivolumab + ipilimumab arm. This was confirmed by clinical experts (Appendix N). Finally, owing to the absence of stratification by PD-L1 expression in CheckMate-743 and the small sample size and event counts in the PD-L1–negative subgroup resulting in wide CIs, the statistical analyses in the PD-L1 subgroups are descriptive in nature and should be interpreted with caution.[4]

Progression-free survival by PD-L1 expression

For PFS per BICR, a benefit of nivolumab + ipilimumab compared with PDC was observed in patients with PD-L1–positive tumours (HR, 0.81; 95% CI, 0.64-1.01), while patients with PD-L1–negative tumours had a PFS HR of 1.79 (95% CI, 1.21-2.64) favouring PDC (see Table 15). However, only 135 patients were included in the PD-L1 < 1% subgroup compared with 451 patients in the PD-L1 ≥ 1% subgroup, which led to limited event counts in the context of time-to-event analyses.[4]

Objective response rate by PD-L1 expression

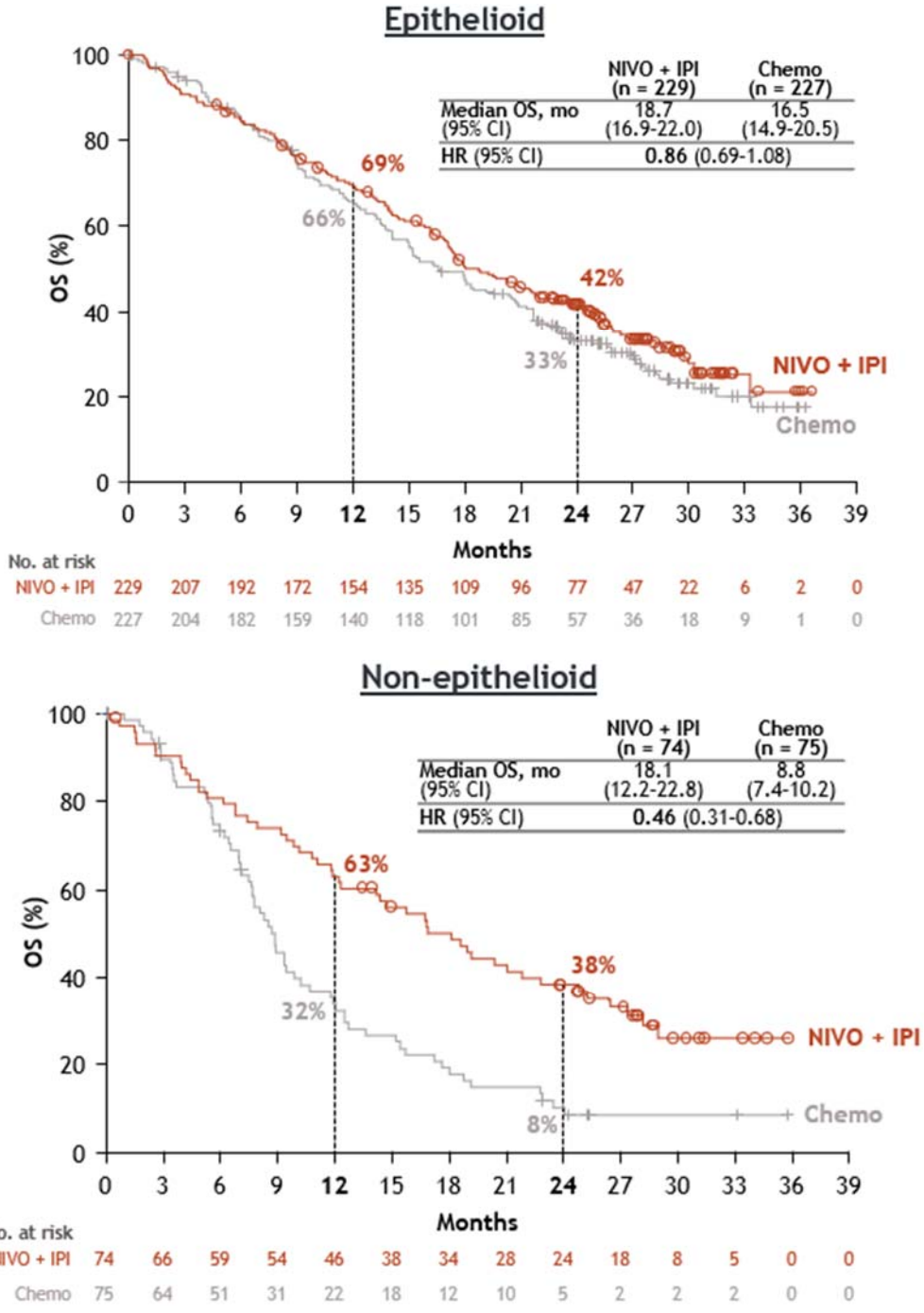
Consistent with all randomised patients, ORR per BICR was similar in both treatment arms in patients with PD-L1–positive tumours. The ORR in patients with PD-L1–negative tumours was numerically lower for nivolumab + ipilimumab compared with PDC (21.1% vs. 38.5%) (see Table 15).[4]

B.2.6.1.5 Secondary endpoint: efficacy by histological subtype

Overall survival by histology

Regardless of histology, patients treated with nivolumab + ipilimumab demonstrated an improvement in OS than those treated with PDC. The observed treatment effect of nivolumab + ipilimumab versus PDC was greater in patients with non-epithelioid MPM than in patients with epithelioid MPM (HR, 0.46 vs. 0.86) (Figure 17). In patients treated with nivolumab + ipilimumab arm, the median OS were similar across histologies (18.70 and 18.10 months for epithelioid and non-epithelioid, respectively). In patients treated with PDC, the median OS was lower in the non-epithelioid versus epithelioid subgroup (8.80 vs. 16.50 months), confirming histology as a prognostic factor in MPM patients receiving PDC.[18]

Figure 17. CheckMate-743: Kaplan-Meier plot of overall survival by histology[a]—all randomised patients



CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival.

Notes: *Chemo* in figure refers to platinum-based doublet chemotherapy. Minimum follow-up was 22.1 months; median follow-up: 29.7 months.

Patients were stratified by tumour histology: epithelioid vs. non-epithelioid. OS HR (95% CI) for epithelioid vs. non-epithelioid were: NIVO + IPI, 0.93 (0.68-1.28); PDC, 0.47 (0.35-0.63).

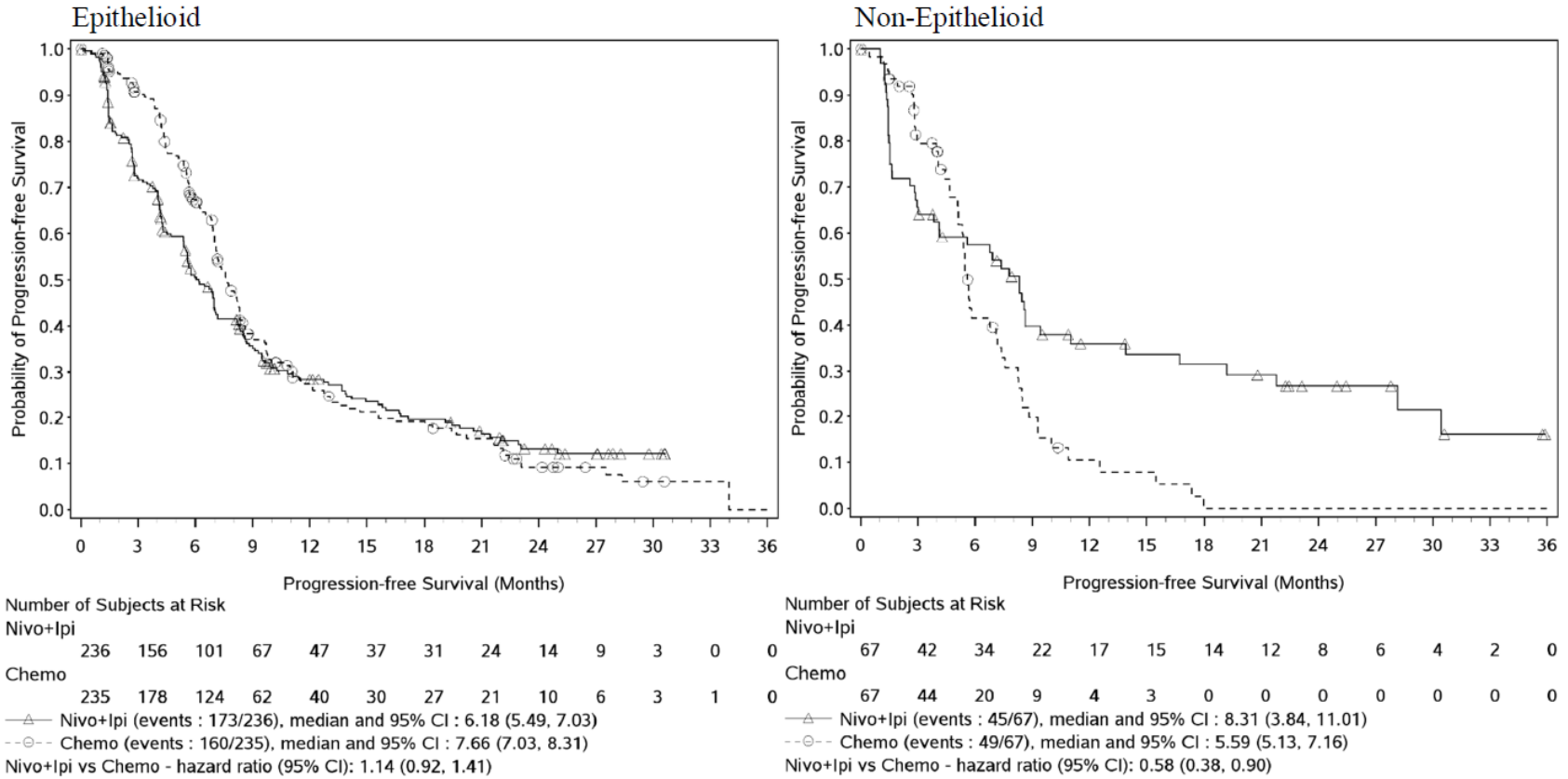
[a] Histology per CRF source.

Source: Baas[18]

Progression-free survival by histology

In patients with non-epithelioid MPM, treatment with nivolumab + ipilimumab resulted in improvement in PFS when compared with treatment with PDC (HR, 0.58; 95% CI, 0.38-0.90), whereas, in patients with epithelioid MPM, treatment with PDC resulted in improvement in PFS over nivolumab + ipilimumab (HR, 1.14; 95% CI, 0.92-1.41) (Figure 18). In patients treated with nivolumab + ipilimumab, the median PFS was longer in non-epithelioid versus epithelioid subgroup (8.31 vs. 6.18 months). On the contrary, in patients treated with PDC, the median PFS was shorter in non-epithelioid versus epithelioid subgroup (5.59 vs. 7.66 months).[4]

Figure 18. CheckMate-743: Kaplan-Meier plot of progression-free survival by histology per interactive response technologies—all randomised patients



CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PFS = progression-free survival.

Notes: *Chemo* in figure refers to platinum-based doublet chemotherapy. Statistical model for hazard ratio: unstratified Cox proportional hazards model. Symbols represent censored observations.

Source: Bristol-Myers Squibb[4]

B.2.6.1.6 Health-related quality of life endpoints

Patients who received first-line nivolumab + ipilimumab experienced stable or improved HRQOL over the treatment period when compared with patients who received PDC, who experienced deterioration in HRQOL over the treatment and follow-up period, as measured by the EQ-5D-3L Utility Index, EQ-5D-3L VAS, and LCSS-Meso scales.[4,78]

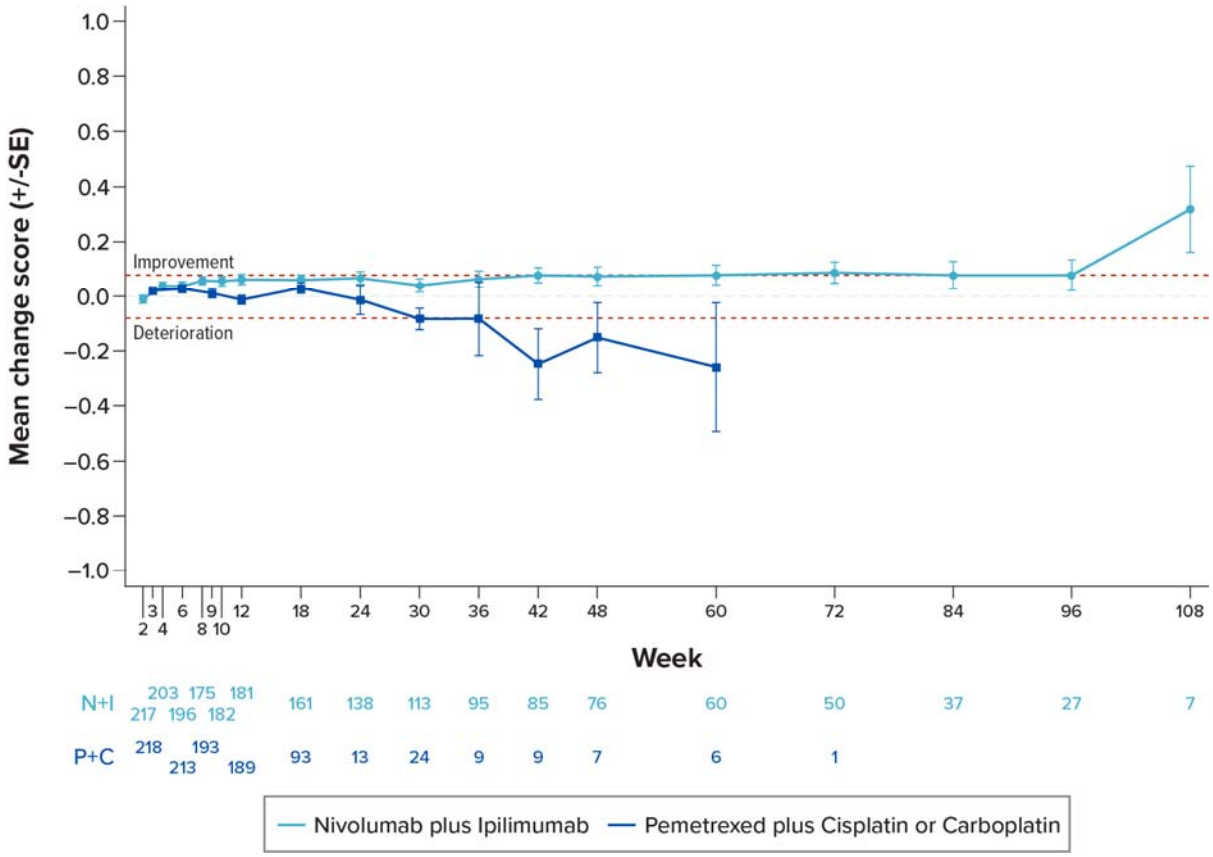
EQ-5D-3L Utility Index

Patients' overall health was assessed using the EQ-5D-3L Utility Index values, which were computed using a scoring algorithm based on the UK time-trade-off value set. The MID, defined as the smallest change considered to be clinically meaningful, has been estimated to be a change from baseline of 0.08 for the EQ-5D-3L Utility Index score.[4]

The mean change in EQ-5D-3L Utility Index scores over time indicated that patients treated with nivolumab + ipilimumab showed improved EQ-5D scores from baseline. In contrast, patients treated with PDC remained stable until week 30 after which a deterioration in scores from baseline was observed (Figure 19).[4,78]

The mean EQ-5D-3L Utility Index scores improved gradually in the nivolumab + ipilimumab arm, from 0.6959 at baseline to a peak score of 0.8529 at week 84. At week 72, a clinically meaningful improvement in EQ-5D-3L Utility Index was observed in the nivolumab + ipilimumab arm (mean change from baseline exceeded the MID of +0.08). The mean EQ-5D-3L Utility Index scores increased slowly in the PDC arm, from 0.7119 at baseline to a peak score of 0.7910 at week 24, before decreasing and falling below baseline starting at week 30. At week 30 a clinically meaningful deterioration in EQ-5D-3L Utility Index was observed in the PDC arm (mean change from baseline exceeded the MID of −0.08).[4]

Figure 19. EQ-5D-3L Utility Index: mean change from baseline scores by treatment group (patient-reported outcome analysis population)



N+I = nivolumab + ipilimumab; P+C = pemetrexed + cisplatin or carboplatin; PRO = patient-reported outcome; SE = standard error.

Note: PRO analysis population includes all patients with EQ-5D baseline data and data at 1 or more postbaseline visits. The EQ-5D Utility Index score ranges from −0.594 to 1, with higher scores indicating better health state. Only time points with > 5 patients are shown.

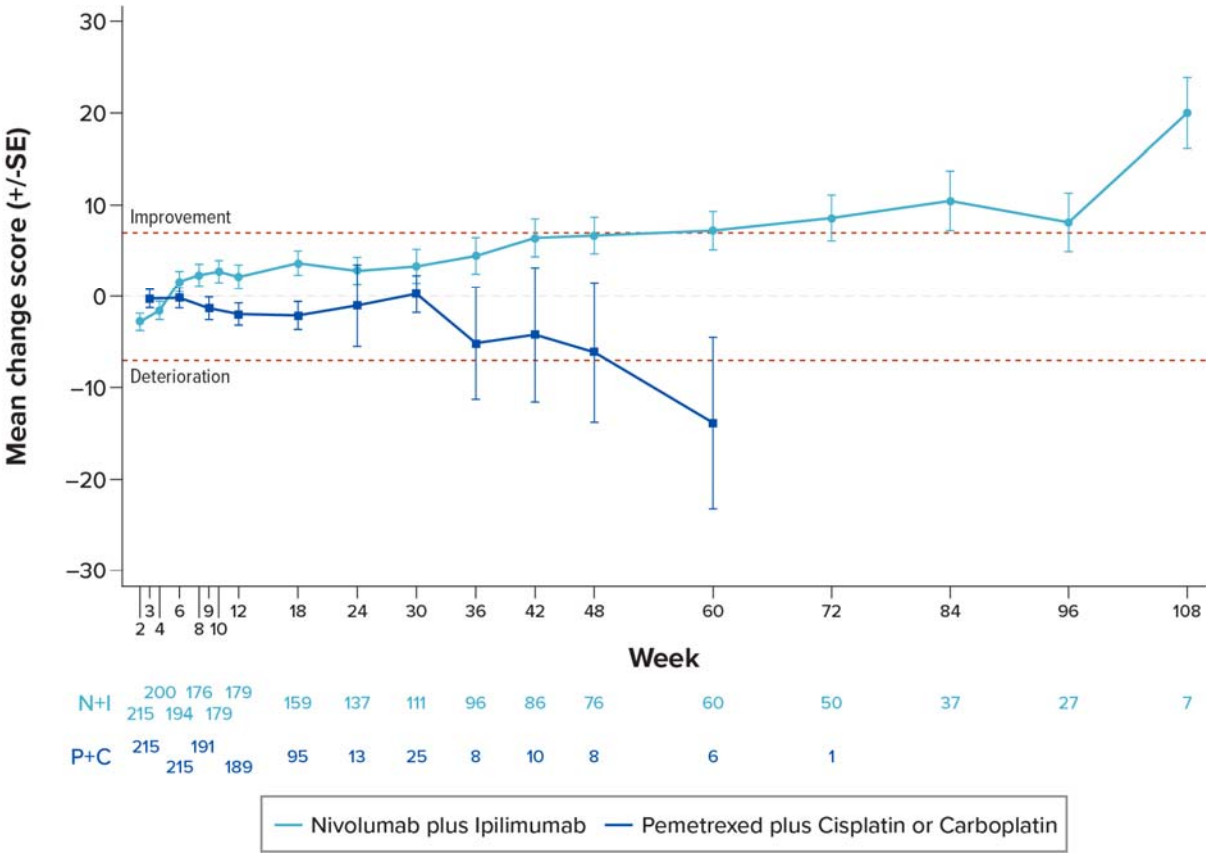
Source: Bristol-Myers Squibb[78]

EQ-5D-3L Visual Analogue Scale

Patients' overall health was also assessed using the EQ-5D VAS. The EQ-5D VAS elicits patients' ratings of their health status on a 0 to 100 scale, with 0 being the worst imaginable health state and 100 being the best imaginable health state. A change from baseline of 7 for the EQ-5D-3L VAS was considered to be the MID.[4]

Figure 20 shows mean change in EQ-5D VAS scores from baseline in CheckMate-743. Generally, a trend for improvement was observed in the nivolumab + ipilimumab arm, which was clinically meaningful from week 60. The mean EQ-5D VAS score increased from 69.9 at baseline to a peak score at week 72 of 82.7. Clinically meaningful improvements (mean score change > 7 points) were observed from weeks 60 through 96.[4] The PDC arm showed stability in scores with a trend for deterioration from week 3 to week 24, and from week 36 to week 60. However, the deterioration was not clinically meaningful.[4] Later in the follow-up period, clinically meaningful deterioration was observed in the PDC arm, but not in the nivolumab + ipilimumab arm (Figure 20).[78]

Figure 20. EQ-5D VAS: mean change from baseline scores by treatment group (patient-reported outcome analysis population)



N+I = nivolumab + ipilimumab; P+C = pemetrexed + cisplatin or carboplatin; PRO = patient-reported outcome; SE = standard error; VAS = visual analogue score.

Note: PRO analysis population includes all patients with EQ-5D baseline data and data at 1 or more postbaseline visits. The EQ-5D VAS score ranges from 0-100, with higher scores indicating better health state. Only time points with > 5 patients are shown.

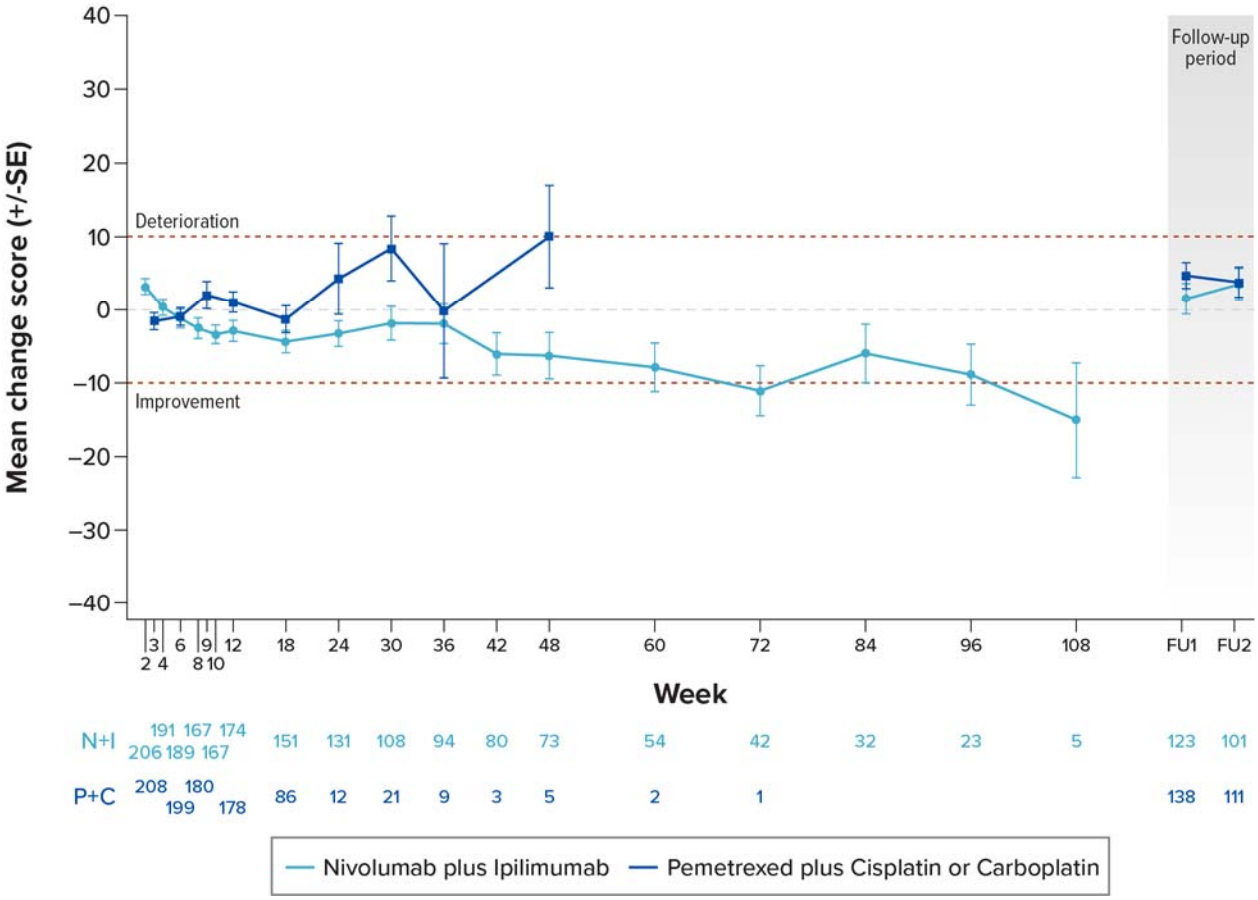
Source: Bristol-Myers Squibb[78]

Lung Cancer Symptom Scale–Mesothelioma (LCSS-Meso) scores

The patient portion of the LCSS-Meso includes five symptom-specific questions that address cough, dyspnoea, fatigue, pain, and anorexia that make up the LCSS-Meso Average Symptom Burden Index (ASBI) and three HRQOL items for symptom distress, activity level, and global HRQOL that make up the LCSS-Meso 3-Item Global Index (3IGI). The scores range from 0 to 100, with 0 representing no symptomatology or highest QOL and 100 being the worst symptomatology or QOL. Clinically meaningful changes in LCSS-Meso ASBI and LCSS-Meso 3IGI scores were defined as 10 and 30 points, respectively.[78]

Results of the LCSS-Meso ASBI showed that patients treated with nivolumab + ipilimumab experienced decreased scores with a clinically meaningful improvement in mean score change from baseline to week 72, while the PDC arm showed stability in scores during treatment (Figure 21).[4,78]

Figure 21. LCSS-Meso ASBI mean change from baseline (patient-reported outcome analysis population)



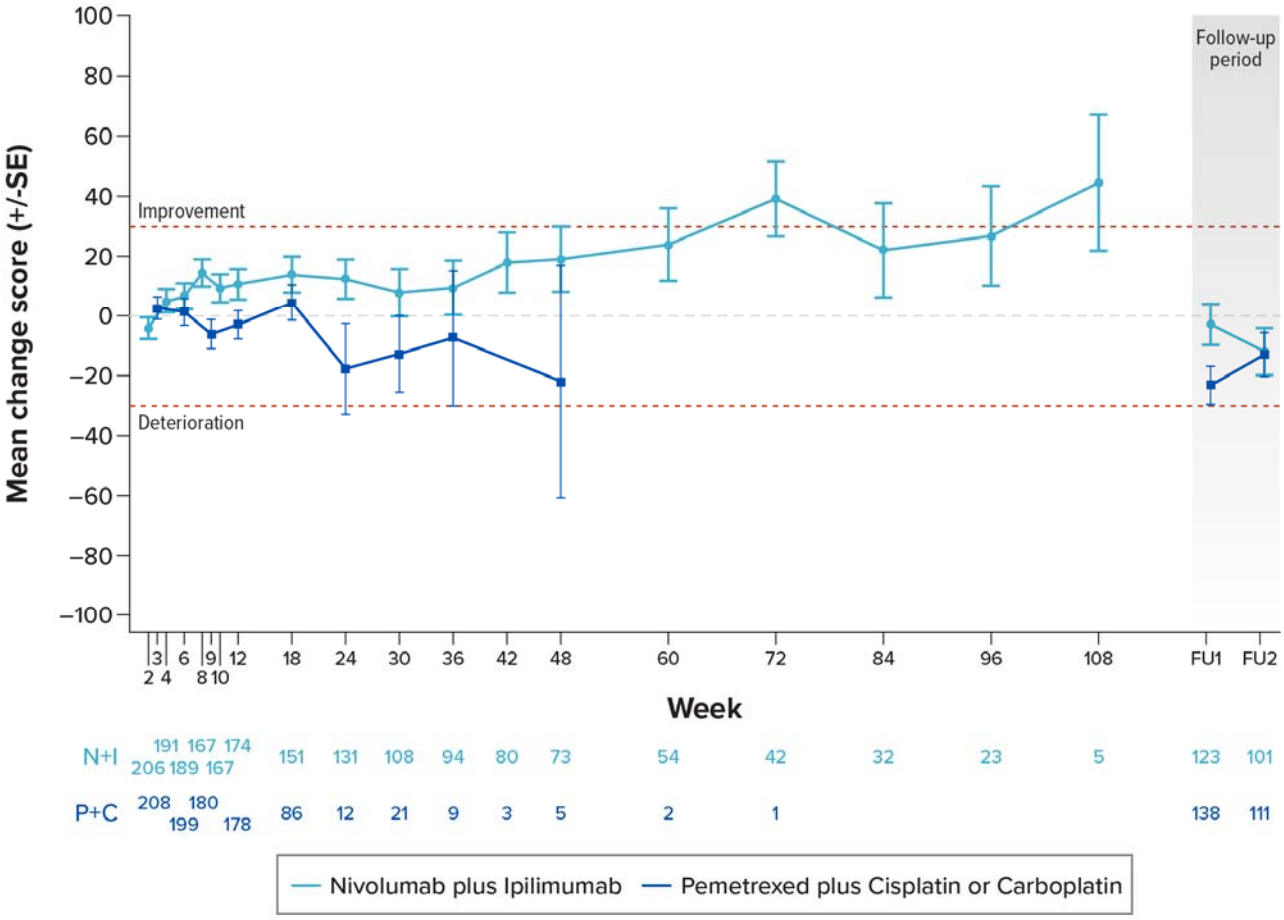
ASBI = Average Symptom Burden Index; LCSS-Meso = Lung Cancer Symptom Scale–Mesothelioma; N+I = nivolumab + ipilimumab; P+C = pemetrexed + cisplatin or carboplatin; PRO = patient-reported outcome; SE = standard error.

Note: PRO analysis population includes all patients with LCSS-Meso baseline data and data at 1 or more postbaseline visits. LCSS-Meso ASBI score is the mean of the symptom-specific questions (items 1-5) and ranges from 0-100, with 0 being the best possible score and 100 being the worst possible score.

Source: Bristol-Myers Squibb[78]

Results of the LCSS-Meso 3IGI showed that patients treated with nivolumab + ipilimumab experienced increased scores with a clinically meaningful improvement in mean score change from baseline to week 72, while the PDC arm showed stability in scores during treatment (Figure 22).[4,78]

Figure 22. LCSS-Meso 3IGI mean change from baseline (patient-reported outcome analysis population)



3IGI = 3-Item Global Index; HRQOL = health-related quality of life; LCSS-Meso = Lung Cancer Symptom Scale–Mesothelioma; N+I = nivolumab + ipilimumab; P+C = pemetrexed + cisplatin or carboplatin; PRO = patient-reported outcomes; SE = standard error.

Note: PRO analysis population includes all patients with LCSS-Meso baseline data and data at 1 or more postbaseline visits. LCSS-Meso 3IGI score is the sum of the 3 summary HRQOL items (items 6-8) and ranges from 0-300, with 0 being the worst possible score and 300 being the best possible score. Only time points with > 5 patients are shown.

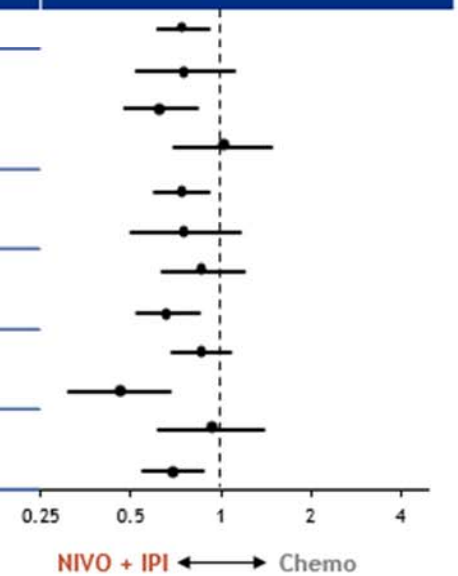
Source: Bristol-Myers Squibb[78]

B.2.7 Subgroup analysis

Figure 23 presents prespecified subgroup analyses for the primary endpoint of OS. The OS benefit observed for nivolumab + ipilimumab compared with PDC in the whole population was also observed across most predefined subgroups, except for patients with aged ≥ 75 years. Further detail for subgroups defined as secondary outcomes is provided in Sections B.2.6.1.4 and B.2.6.1.5. Additional efficacy results by subgroup are presented in Appendix F.

Figure 23. CheckMate-743: overall survival, subgroup analysis

Subgroup	Median OS, mo		Unstratified HR	Unstratified HR (95% CI)
	NIVO + IPI n = 303	Chemo n = 302		
All randomized (N = 605)	18.1	14.1	0.75[a]	
< 65 years (n = 167)	17.2	13.3	0.76	
≥ 65 to < 75 years (n = 281)	20.3	14.9	0.63	
≥ 75 years (n = 157)	16.9	15.4	1.02	
Male (n = 467)	17.5	13.7	0.74	
Female (n = 138)	21.4	18.0	0.76	
ECOG performance status 0 (n = 242)	20.7	19.5	0.87	
ECOG performance status ≥ 1 (n = 363)	17.0	11.6	0.66	
Epithelioid (n = 456)	18.7	16.5	0.86	
Non-epithelioid (n = 149)	18.1	8.8	0.46	
PD-L1 < 1% (n = 135)	17.3	16.5	0.94	
PD-L1 ≥ 1% (n = 451)	18.0	13.3	0.69	



CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PD-L1 = programmed death-ligand 1.

Note: *Chemo* in figure refers to platinum-based doublet chemotherapy.

[a] Stratified HR, 0.74.

Source: Baas[18]

B.2.8 Meta-analysis

Only one RCT (CheckMate-743) was identified via the SLR that has investigated the efficacy and safety of nivolumab + ipilimumab for the first-line treatment of MPM. As such, a meta-analysis could not be conducted, as this would require two or more studies that contained the intervention of interest.

B.2.9 Indirect and mixed treatment comparisons

CheckMate-743 provided head-to-head trial evidence of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin; thus, it included all the UK-relevant comparators of interest that are deemed appropriate by clinical experts (see Decision problem, Section B.1.1). As CheckMate-743 provides the highest quality head-to-head evidence with all appropriate comparators, an indirect treatment comparison was not deemed necessary to support the clinical effectiveness of nivolumab + ipilimumab for this submission.

B.2.10 Adverse reactions

B.2.10.1 CheckMate-743: safety overview

Safety data are presented for all treated patients in CheckMate-743 by treatment arm: nivolumab + ipilimumab for up to 2 years or pemetrexed + cisplatin or carboplatin chemotherapy given for up to 6 cycles. As the maximum duration of treatment per protocol for nivolumab + ipilimumab was 2 years versus 6 cycles for PDC, the median duration of treatment was longer for the nivolumab + ipilimumab arm than for the PDC arm: 5.6 months (IQR, 2.0-11.4 months) versus 3.5 months (2.7-3.7 months), respectively.[18] Most patients in both treatment arms received ≥ 90% of planned doses. Table 16 presents the cumulative number of doses by each component in each treatment arm.

Table 16. CheckMate-743: cumulative dose and relative dose intensity

	Nivolumab + ipilimumab (n = 300)		PDC (n = 284)		
	Nivolumab (n = 300)	**Ipilimumab (n = 300)**	**Pemetrexed (n = 284)**	**Cisplatin (n = [redacted])**	**Carboplatin (n = [redacted])**
Number of doses received					
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (IQR)	12.0 (5.0-23.5)	4.0 (2.0-7.0)	6.0 (4.0-6.0)	5.0 (3.0-6.0)	6.0 (4.0-6.0)
Cumulative dose (unit)[a]					
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity (%)					
≥ 110%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90% to < 110%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70% to < 90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50% to < 70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
< 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AUC = area under the curve; IQR = interquartile range; PDC = platinum-based doublet chemotherapy.

[a] Dose units: nivolumab and ipilimumab in milligrams per kilograms; cisplatin and pemetrexed in milligrams per square metre; and carboplatin in AUC.

Sources: Baas[18]; Bristol-Myers Squibb[4]

B.2.10.2 CheckMate-743: overall safety profile

The safety profile of nivolumab + ipilimumab in first-line MPM was consistent with that previously seen at this dose and schedule in MPM and in other indications, and no new safety signals or toxicities were observed.

The overall frequencies of all-causality AEs and treatment-related AEs (TRAEs) were similar between treatment arms. Frequencies of grade 3-4 AEs (all causality) were higher with nivolumab + ipilimumab compared with PDC, but frequencies of grade 3-4 TRAEs were similar between the treatment arms (Table 17).

Table 17. CheckMate-743: safety summary—all treated patients

	Nivolumab + ipilimumab (n = 300)		PDC (n = 284)	
Safety parameters, n (%)	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
All-causality SAEs	164 (54.7)	103 (34.3)	72 (25.4)	54 (19.0)
Treatment-related SAEs	64 (21.3)	46 (15.3)	22 (7.7)	17 (6.0)
All-causality AEs leading to discontinuation	88 (29.3)	59 (19.7)	58 (20.4)	28 (9.9)
Treatment-related AEs leading to discontinuation	69 (23.0)	45 (15.0)	45 (15.8)	21 (7.4)
All-causality AEs	299 (99.7)	159 (53.0)	277 (97.5)	121 (42.6)
Treatment-related AEs	240 (80.0)	91 (30.3)	233 (82.0)	91 (32.0)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PDC = platinum-based doublet chemotherapy; SAE = severe adverse event.

Note: Definitions of events were based on MedDRA version 22.1; Common Terminology Criteria version 4.0. Includes events reported between first dose and 30 days after the last dose of study drug, unless otherwise indicated.

Sources: Baas[18]; Bristol-Myers Squibb[4]

Overall rates of TRAEs were similar between treatment arms, but the types of AEs differed, which was consistent with the different mechanisms of action of each regimen (Table 18). The most common TRAEs (≥ 15%) with nivolumab + ipilimumab were diarrhoea (21%) and pruritus (16%); with PDC, these were nausea (37%), anaemia (36%), neutropenia (25%), fatigue (19%), decreased appetite (18%), and asthenia (16%). When compared with PDC, nivolumab + ipilimumab was associated with substantially lower rates of TRAEs typically associated with chemotherapy, such as nausea, anaemia, and neutropenia.[18] Any grade of TRAEs causing discontinuation occurred in 23% of patients treated with nivolumab + ipilimumab and 16% of patients treated with PDC. Table 18 describes TRAEs in CheckMate-743 for all treated patients.

Table 18. CheckMate-743: treatment-related adverse events—all treated patients

	Nivolumab + ipilimumab[a] (n = 300)		PDC[b] (n = 284)	
Safety parameters, n (%)	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
TRAEs leading to discontinuation of any component of the regimen[c]	69 (23.0)	45 (15.0)	45 (15.8)	21 (7.4)
Serious TRAEs[c]	64 (21.3)	46 (15.3)	22 (7.7)	17 (6.0)
Any TRAE[c]	240 (80.0)	91 (30.3)	233 (82.0)	91 (32.0)
≥ 15% of patients in any treatment group				
Diarrhoea	62 (20.7)	10 (3.3)	21 (7.4)	2 (0.7)
Pruritus	49 (16.3)	3 (1.0)	1 (0.4)	0
Fatigue	41 (13.7)	3 (1.0)	55 (19.4)	5 (1.8)
Nausea	30 (10.0)	1 (0.3)	104 (36.6)	7 (2.5)
Decreased appetite	29 (9.7)	2 (0.7)	50 (17.6)	2 (0.7)
Asthenia	25 (8.3)	0	44 (15.5)	12 (4.2)
Anaemia	6 (2.0)	1 (0.3)	102 (35.9)	32 (11.3)
Neutropenia	2 (0.7)	2 (0.7)	71 (25.0)	43 (15.1)
Treatment-related select AEs				
Endocrine	52 (17.3)	4 (1.3)	0	0
Gastrointestinal	66 (22.0)	16 (5.3)	23 (8.1)	3 (1.1)
Hepatic	36 (12.0)	16 (5.3)	6 (2.1)	0
Pulmonary	20 (6.7)	2 (0.7)	0	0
Renal	15 (5.0)	4 (1.3)	19 (6.7)	1 (0.4)
Skin	108 (36.0)	9 (3.0)	28 (9.9)	1 (0.4)
Hypersensitivity/infusion reactions	36 (12.0)	4 (1.3)	7 (2.5)	0

AE = adverse event; PDC = platinum-based doublet chemotherapy; TRAE = treatment-related adverse event.

Note: Person-years of exposure: nivolumab + ipilimumab, 220.3; chemotherapy, 94.5. Nivolumab + ipilimumab dosages were nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks.

[a] Median (interquartile range) doses for treated patients: nivolumab, 12.0 (5.0-23.5); ipilimumab, 4.0 (2.0-7.0).

[b] Median (interquartile range) doses for treated patients: pemetrexed, 6.0 (4.0-6.0); cisplatin 5.0 (3.0-6.0); carboplatin 6.0 (4.0-6.0).

[c] Includes events reported between first dose and 30 days after last dose of study drug.

Sources: Baas[18]; Bristol-Myers Squibb[4]

The overall frequencies of all-causality AEs were similar between the nivolumab + ipilimumab (100%) and PDC (98%) arms, although the types of AEs differed, which was consistent with the mechanism of action of each treatment. Frequencies of all-causality grade 3-4 AEs were higher with nivolumab + ipilimumab (53%) compared with PDC (43%).[4] The frequencies of all-causality SAEs and AEs leading to discontinuation were higher with nivolumab + ipilimumab compared with PDC. Table 19 presents the safety summary for all treated patients.

Table 19. CheckMate-743: all-causality adverse events—all treated patients

	Nivolumab + ipilimumab[a] (n = 300)		PDC[b] (n = 284)	
Safety parameters, n (%)	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
All-causality SAEs	164 (54.7)	103 (34.3)	72 (25.4)	54 (19.0)
All-causality AEs leading to discontinuation	88 (29.3)	59 (19.7)	58 (20.4)	28 (9.9)
All-causality AEs	299 (99.7)	159 (53.0)	277 (97.5)	121 (42.6)
≥ 20% of patients in any treatment group				
Diarrhoea	94 (31.3)	12 (4.0)	32 (11.3)	2 (0.7)
Fatigue	86 (28.7)	9 (3.0)	77 (27.1)	5 (1.8)
Dyspnoea	78 (26.0)	7 (2.3)	41 (14.4)	9 (3.2)
Nausea	73 (24.3)	2 (0.7)	123 (43.3)	7 (2.5)
Decreased appetite	71 (23.7)	3 (1.0)	72 (25.4)	4 (1.4)
Anaemia	43 (14.3)	8 (2.7)	119 (41.9)	39 (13.7)
Constipation	56 (18.7)	1 (0.3)	84 (29.6)	2 (0.7)
Neutropenia	5 (1.7)	3 (1.0)	79 (27.8)	45 (15.8)
Asthenia	49 (16.3)	4 (1.3)	57 (20.1)	12 (4.2)
Cough	65 (21.7)	2 (0.7)	22 (7.7)	0
Pruritus	62 (20.7)	3 (1.0)	4 (1.4)	0
Rash	60 (20.0)	3 (1.0)	21 (7.4)	0
All-causality select AEs				
Endocrine	62 (20.7)	6 (2.0)	7 (2.5)	1 (0.4)
Gastrointestinal	97 (32.3)	18 (6.0)	34 (12.0)	3 (1.1)
Hepatic	54 (18.0)	19 (6.3)	9 (3.2)	0
Pulmonary	26 (8.7)	6 (2.0)	2 (0.7)	1 (0.4)
Renal	33 (11.0)	6 (2.0)	25 (8.8)	3 (1.1)
Skin	136 (45.3)	11 (3.7)	42 (14.8)	1 (0.4)
Hypersensitivity/infusion reactions	37 (12.3)	4 (1.3)	7 (2.5)	0

AE = adverse event; SAE = serious adverse event; TRAE = treatment-related adverse event.

Note: Person-years of exposure: nivolumab + ipilimumab, 220.3; chemotherapy, 94.5. Nivolumab + ipilimumab dosages were nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks.

[a] Median (interquartile range) doses for treated patients: nivolumab, 12.0 (5.0-23.5); ipilimumab, 4.0 (2.0-7.0).

[b] Median (interquartile range) doses for treated patients: pemetrexed, 6.0 (4.0-6.0); cisplatin 5.0 (3.0-6.0); carboplatin 6.0 (4.0-6.0).

Source: Bristol-Myers Squibb[4]

Select AEs of special interest and IMAEs, including those that were severe (grade 3-4), were manageable using the established treatment algorithms. Most treatment-related select AEs and most IMAEs with nivolumab + ipilimumab had resolved at the time of database lock, except for endocrine events. The median time to resolution ranged from 0.14 to 12.14 weeks for select AEs and from 0.14 to 17.14 weeks for IMAEs. Most laboratory abnormalities (haematology, liver tests, kidney function tests, and electrolytes) were grade 1 and 2 in both arms. There was a higher frequency of elevated alanine aminotransferase/aspartate

transaminase (AST/ALT) and abnormal increases or decreases in thyroid-stimulating hormone (TSH) with nivolumab + ipilimumab treatment and a higher frequency of haematologic abnormalities with PDC. Most haematology and liver test abnormalities were grade 1-2.[4] Table 20 presents the summary of IMAEs and other events of special interest.

Table 20. CheckMate-743: summary of immune-mediated adverse events and other events of special interest—all treated patients

	Nivolumab + ipilimumab[a] (n = 300)		PDC[b] (n = 284)	
Safety parameters, n (%)	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
All-causality IMAEs within 100 days of last dose treated with immune-modulating medication	164 (54.7)	103 (34.3)	72 (25.4)	54 (19.0)
Diarrhoea/colitis	26 (8.7)	12 (4.0)	1 (0.4)	1 (0.4)
Hepatitis	18 (6.0)	14 (4.7)	0	0
Pneumonitis	20 (6.7)	6 (2.0)	0	0
Nephritis/renal dysfunction	8 (2.7)	5 (1.7)	0	0
Rash	39 (13.0)	8 (2.7)	3 (1.1)	0
Hypersensitivity/infusion reactions	5 (1.7)	1 (0.3)	0	0
All-causality endocrine IMAEs within 100 days of last dose with or without immune-modulating medication				
Adrenal insufficiency	7 (2.3)	2 (0.7)	0	0
Hypophysitis	12 (4.0)	3 (1.0)	0	0
Hypothyroidism/thyroiditis	35 (11.7)	0	1 (0.4)	0
Hyperthyroidism	11 (3.7)	0	1 (0.4)	0
Diabetes mellitus	1 (0.3)	1 (0.3)	0	0
All-causality OESIs within 100 days of last dose with or without immune-modulating medication				
Pancreatitis	4 (1.3)	1 (0.3)	0	0
Encephalitis	3 (1.0)	1 (0.3)	1 (0.4)	1 (0.4)
Myositis	2 (0.7)	2 (0.7)	0	0
Myasthenic syndrome	2 (0.7)	2 (0.7)	0	0
Demyelination	0	0	0	0
Guillain-Barré syndrome	0	0	0	0
Uveitis	2 (0.7)	1 (0.3)	0	0
Myocarditis	1 (0.3)	1 (0.3)	0	0
Rhabdomyolysis	0	0	0	0
Graft versus host disease	0	0	0	0

IMAE = immune-mediated adverse event; OESI = other event of special interest; PDC = platinum-based doublet chemotherapy.

Note: Definitions of events were based on MedDRA version 22.1; Common Terminology Criteria version 4.0. Includes events reported between first dose and 30 days after the last dose of study drug, unless otherwise indicated.

[a] Median (interquartile range) doses for treated patients: nivolumab, 12.0 (5.0-23.5); ipilimumab, 4.0 (2.0-7.0).

[b] Median (interquartile range) doses for treated patients: pemetrexed, 6.0 (4.0-6.0); cisplatin 5.0 (3.0-6.0); carboplatin 6.0 (4.0-6.0).

Source: Bristol-Myers Squibb[4]

As of the 3 April 2020 database lock, 198 patients (66%) who received nivolumab + ipilimumab and 212 (75%) who received PDC had died. Disease progression was the most common cause of death in both arms. The frequency of treatment-related deaths was low and similar between the two arms.[4] Table 21 presents the death summary for all treated patients.

Table 21. CheckMate-743: summary of deaths—all treated patients

Safety parameters, n (%)	Nivolumab + ipilimumab[a] (n = 300)	Chemotherapy[b] (n = 284)
Number of patients who died	198 (66.0)	212 (74.6)
Within 30 days of last dose	28 (9.3)	14 (4.9)
Within 100 days of last dose	55 (18.3)	50 (17.6)
Primary reason for death		
Disease	183 (61.0)	199 (70.1)
Study drug toxicity	3 (1.0)[c]	1 (0.4)[d]
Unknown	3 (1.0)	2 (0.7)
Other	9 (3.0)	10 (3.5)

Note: Person-years of exposure: nivolumab + ipilimumab, 220.3; chemotherapy, 94.5. Nivolumab + ipilimumab dosages were nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks.

[a] Median (interquartile range) doses for treated patients: nivolumab, 12.0 (5.0-23.5); ipilimumab, 4.0 (2.0-7.0).

[b] Median (interquartile range) doses for treated patients: pemetrexed, 6.0 (4.0-6.0); cisplatin 5.0 (3.0-6.0); carboplatin 6.0 (4.0-6.0).

[c] 3 deaths due to nivolumab + ipilimumab: pneumonitis, encephalitis, and acute heart failure.

[d] 1 death due to chemotherapy: myelosuppression.

Sources: Baas[18]; Bristol-Myers Squibb[4]

B.2.11 Ongoing studies

CheckMate-743 is ongoing, and a final primary OS analysis will be conducted when 473 deaths have occurred (estimated date for primary completion: April 2021; study final completion date: April 2022).[4,74] Additional data cuts anticipated over the next 12 to 18 months will provide further evidence of the long-term benefit associated with nivolumab + ipilimumab over current SOC and reduce the uncertainty around long-term survival (Table 22).

Table 22. Additional data anticipated from CheckMate trials in the next 12 months

Trial	Next anticipated data lock	Analyses anticipated
CheckMate-743	[redacted]	Additional follow-up for OS for nivolumab + ipilimumab vs. PDC

Abbreviations: OS = overall survival; PDC = platinum-based doublet chemotherapy.

In addition, real-world data could be collected through the Systemic Anti-Cancer Therapy (SACT) and other real-world data sets. BMS plan to leverage secondary data from I-O Optimise, a pan-European evidence platform that brings together real-word data sources under independent scientific guidance. Data analyses are ongoing with continuous creation of new cohorts to capture changes over time. This includes the analysis of UK registry data.

B.2.12 Innovation

- MPM is a rare, occupational-related lung cancer caused by asbestos exposure, and the UK is currently at the peak incidence for MPM.
- All patients with MPM have a poor prognosis, and there is a high unmet need. Patients with MPM have a short life expectancy, and the only approved treatment available is PDC, which is of limited clinical benefit with poor tolerability. This patient population is often elderly and frail, which means up to 60% of patients are ineligible for SACT who therefore only receive BSC.[32]
- There is no innovative immunotherapy approved for use, with little progress in improved survival and no new therapies approved for use in the last two decades.[24]
  - Targeted vascular endothelial growth factor (VEGF) inhibitor therapy with bevacizumab has been investigated for treatment of MPM, but it is not approved for use.
  - There have been multiple failed trials of new therapies in this indication (vorinostat, nintedanib [LUME-Meso], pembrolizumab [PROMISE-Meso], defactinib, tremelimumab).
  - There are no new drugs on the horizon, as ongoing trials with newer therapies and combinations (durvalumab, pembrolizumab ± anetumab, atezolizumab + bevacizumab) are still in early development, with results of phase 3 trials not expected until 2022-2024.
- Nivolumab + ipilimumab is a first-in-class immunotherapy for MPM. The innovative combination of using two immunotherapies to treat patients with MPM harnesses the complementary antitumour modes of action of both nivolumab and ipilimumab.
- The Medicines and Healthcare Products Regulatory Agency (MHRA) awarded nivolumab + ipilimumab a Promising Innovative Medicine (PIM) designation in MPM, and an Early Access to Medicines Scheme (EAMS) is planned to open in early 2021.
- Nivolumab + ipilimumab represents a step change in the management of MPM and, if adopted, would replace the current standard first-line PDC, pemetrexed + cisplatin or carboplatin. Nivolumab + ipilimumab would provide an innovative chemotherapy-free immunotherapy with significant survival benefits and improved tolerability versus PDC. The current SOC PDC regimens are associated with significant risks of myelosuppression and infection, which are not observed with immunotherapy.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Summary of the clinical evidence

- CheckMate-743 is the first positive randomised trial of any immunotherapy for the first-line treatment of patients with unresectable MPM. A prespecified interim analysis of efficacy data showed a highly significant OS benefit, increased duration of response, and improvements in patient HRQOL with nivolumab + ipilimumab versus PDC[18] in all patients included in this appraisal:

  - Nivolumab + ipilimumab demonstrated a statistically and clinically significant improvement in OS versus PDC (HR, 0.74; 96.6% CI, 0.60-0.91; stratified log-rank test, *P* = 0.0020). Median OS was 18.07 months (95% CI, 16.82-21.45 months) and 14.09 months (95% CI, 12.45-16.23 months) for nivolumab + ipilimumab and PDC, respectively. The 24-month OS rate was 40.8% versus 27.0% for nivolumab + ipilimumab versus PDC.
  - Nivolumab + ipilimumab resulted in more durable responses (median, 11.01 vs. 6.67 months) and more CRs than PDC (5 vs. 0).
  - First-line nivolumab + ipilimumab resulted in improvements in HRQOL versus PDC, as measured by the EQ-5D-3L Utility Index, EQ-5D-3L VAS, and LCSS-Meso scales.
- Efficacy with nivolumab + ipilimumab in CheckMate-743 was consistent across subgroups[18]:
  - The OS benefit with nivolumab + ipilimumab versus PDC was greater in patients with PD-L1 ≥ 1% (HR, 0.69; 95% CI, 0.55-0.87) than in patients with PD-L1 < 1% (HR, 0.94; 95% CI, 0.62-1.40). However, within the treatment group, a similar OS benefit was observed with nivolumab + ipilimumab regardless of PD-L1 expression (median OS of 17.3 months in PD-L1 < 1% and 18.0 months in PD-L1 ≥ 1%). PD-L1 was not a stratification factor in CheckMate-743; therefore, the data are limited by potential imbalances in known or unknown prognostic factors because the role of PD-L1 in MPM is unclear. Owing to the small sample size and event counts in the PD-L1–negative subgroup, the statistical analyses in the PD-L1 subgroups are descriptive in nature and should be interpreted with caution.
  - An OS benefit was observed in epithelioid and non-epithelioid subgroups, with similar results for nivolumab + ipilimumab in both histology subgroups. The treatment effect of nivolumab + ipilimumab versus PDC was more pronounced in the non-epithelioid subgroup (HR, 0.46) than in the epithelioid subgroup (HR, 0.86).
- Safety data for nivolumab + ipilimumab in CheckMate-743 show that this regimen is tolerable in MPM. No new safety concerns or toxicities with nivolumab + ipilimumab were identified in CheckMate-743. Overall rates of treatment-related grade 3-4 AEs with nivolumab + ipilimumab and PDC were similar, but nivolumab + ipilimumab was associated with lower rates of AEs typically associated with chemotherapy (nausea, anaemia, and neutropenia).[18]
- CheckMate-743 is ongoing; additional follow-up will further demonstrate the long-term, durable benefit anticipated with dual immunotherapy with nivolumab + ipilimumab versus PDC. Additional maturity of OS data would reduce current uncertainty on the long-term survival benefit. Therefore, BMS consider nivolumab + ipilimumab to be a candidate for entry into the CDF.

B.2.13.2 Strengths and limitations of the clinical evidence base for nivolumab + ipilimumab in MPM

The key clinical evidence for nivolumab + ipilimumab comes from CheckMate-743, a large, international, multicentre, randomised, active-controlled, open-label, phase 3 clinical trial that

included six sites in the UK. CheckMate-743 is ongoing: a published interim analysis reported 89% of the expected events required for the final OS analysis (419 of 473 required OS events). This interim analysis provides high-quality, robust evidence of the clinically relevant survival benefit of nivolumab + ipilimumab compared with PDC in patients with untreated unresectable MPM. The final analysis will provide longer-term survival data and is expected to show a durable treatment effect with dual immunotherapy.

CheckMate-743 is the only phase 3 RCT that compares open-label nivolumab + ipilimumab with PDC for the first-line treatment of MPM. As PDC is the SOC for the first-line treatment of MPM in the NHS in England, the active comparator used in CheckMate-743 (pemetrexed + cisplatin or carboplatin) was deemed appropriate by UK clinical experts (Appendix N). Similar to other immunotherapy trials, CheckMate-743 is being conducted using an open-label (rather than blinded) study design for ethical and safety reasons because the management of similar AEs will differ between treatment arms, given the different mechanisms of action of different treatments. If this trial was blinded, the management of AEs would potentially be delayed or detrimental to the patient.[75] A quality assessment of this RCT (see Section B.2.5 and Appendix D) determined the trial to have a robust overall design and execution, according to the NICE criteria for assessment and risk of bias.[82]

The primary endpoint of CheckMate-743 is OS, which is the most appropriate primary clinical endpoint in studies of MPM, which is an aggressive tumour type with a poor prognosis. However, as CheckMate-743 is ongoing, OS data are not fully mature, so the anticipated long-term, durable OS benefit of dual immunotherapy with nivolumab + ipilimumab is still uncertain. The KM curve for the interim OS analysis showed a trend towards a plateau with nivolumab + ipilimumab, and this is supported by the KM curves for PFS and DOR, which suggest the possibility of a proportion of patients with long-term survival when treated with immunotherapy—this was also highlighted by clinical experts (Appendix N).

The trial population of CheckMate-743 is patients with unresectable MPM, which is representative of this patient population in England, as confirmed by UK clinical experts (Appendix N). The trial includes 38 patients at six sites in the UK where nivolumab + ipilimumab was used to treat MPM in a research setting within UK NHS hospitals using an active comparator that is SOC in England; therefore, results should be generalisable to UK clinical practice. As nivolumab + ipilimumab is already approved for use in other oncology indications, most specialists are used to managing patients on immunotherapy, so it should be easily integrated into routine UK clinical practice.

The dosing and schedule of nivolumab in CheckMate-743 (3 mg/kg every 2 weeks) differs from the proposed indicated dose and schedule of nivolumab submitted to the European Medicines Agency (EMA) (360 mg every 3 weeks). The dose and schedule of ipilimumab (1 mg/kg every 6 weeks) is the same in CheckMate-743 and the proposed indication. Based on the totality of pharmacokinetic modelling of nivolumab exposure, exposure-efficacy, exposure-safety, and clinical subgroup efficacy and safety analyses, the balance of benefits and risks of nivolumab 360 mg every 3 weeks is expected to be similar to that of nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks for the treatment of untreated unresectable MPM. Moreover, this dosing schedule will allow less frequent dosing for patients and clinicians. This dosing schedule for treating first-line MPM

was approved by the FDA on 2 October 2020[85] and is the standard nivolumab dose used in a range of lung cancer indications recommended by NICE, including for the second-line treatment of squamous and non-squamous NSCLC.[86,87]

B.2.13.3 End of life criteria

Nivolumab + ipilimumab fulfils the NICE end of life criteria in all patients with unresectable MPM (Table 23). Most patients die less than 2 years after diagnosis, with a median survival of 13 months in unresectable patients with MPM treated with SACT.[44] Interim results from CheckMate-743 have determined a median 4-month survival benefit with nivolumab + ipilimumab versus PDC, with a median OS follow-up of 29.7 months.[18]

Table 23. End of life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally < 24 months	• 2016-2018 UK National Mesothelioma Audit showed low rates of survival from disease diagnosis: 10% of patients with MPM were alive after 3 years and 40% after 1 year.[32] • Retrospective analysis of the 2013-2017 CAS registry in England (N = 9,458) showed a median OS of 8.3 months (IQR, 3.1-17.2); 1-year OS was 38% (95% CI, 37%-39%), 2-year OS was 16% (95% CI, 15%-16%), and 3-year OS was 8% (95% CI, 7%-9%).[44] –Median OS by histological subtype: sarcomatoid (4.3 months), not specified (5.8 months), biphasic (8.3 months), and epithelioid (13.3 months) –Median OS by treatment: surgery + SACT (21.5 months), unresected + SACT (12.9 months), and BSC (3.8 months)	Section B.1.3.2.3, page 20-21
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months compared with current NHS treatment	CheckMate-743 determined a median 4-month survival benefit with nivolumab + ipilimumab vs. PDC, with a median OS follow-up of 29.7 months. Median OS was 18.1 months (95% CI, 16.8-21.4 months) for nivolumab + ipilimumab vs. 14.1 months (95% CI, 12.4-16.2 months) for PDC.[18]	Section B.2.6.1.2, page 41-43

BSC = best supportive care; CAS = Cancer Analysis System; CI = confidence interval; IQR = interquartile range; MPM = malignant pleural mesothelioma; NHS = National Health Service; OS = overall survival; PDC = platinum-based doublet chemotherapy; SACT = systemic anticancer therapy; UK = United Kingdom; US = United States.

B.3 Cost-effectiveness

SUMMARY OF COST-EFFECTIVENESS

- A de novo partitioned survival model was developed to assess the cost-effectiveness of nivolumab + ipilimumab compared with PDC for adults with untreated unresectable MPM. This is consistent with the population and treatments studied in CheckMate-743.
- Clinical data for modelling nivolumab + ipilimumab and PDC were derived from the CheckMate-743 trial. At the April 2020 database lock of CheckMate-743, the minimum follow-up for all patients was 22.1 months. To estimate OS and PFS over the 20-year model time horizon, survival beyond the study follow-up period had to be informed by extrapolation. As the current survival data from CheckMate-743 are relatively immature, it is anticipated that long-term extrapolations based only on these data would not fully capture the short-term treatment response and long-term survival that are unique for the dual immunotherapy being investigated. Thus, additional data collected through the CDF will be beneficial to inform the long-term outcomes of nivolumab + ipilimumab compared with PDC.
- Duration of treatment with nivolumab + ipilimumab and PDC was modelled directly using time-to-treatment discontinuation and dosing from CheckMate-743. PDC is given for a maximum of 6 cycles and nivolumab + ipilimumab is given for a maximum of 24 months. Health-related quality of life data collected in CheckMate-743 using the EQ-5D-3L were also used in the model. Treatment-specific, progression-based health-state utility values were used in the base-case analysis. Other model input parameters were identified from published literature and standard national sources.
- The results of the cost-effectiveness analysis showed improved survival for patients treated with nivolumab + ipilimumab, resulting in an increase of 0.702 quality-adjusted life-years (QALYs) versus PDC. Based on the current simple patient access schemes (PASs) for nivolumab ([redacted]) and ipilimumab ([redacted]), approved by the Department of Health, this resulted in an incremental cost-effectiveness ratio (ICER) of £77,502 per QALY. The ICER was generally most sensitive to changes in health-state utility weights and drug wastage assumptions.
- In conclusion, nivolumab + ipilimumab offers an innovative, clinically effective treatment option in the first-line MPM setting.

B.3.1 Published cost-effectiveness studies

An SLR was undertaken to identify all cost-effectiveness studies relevant to the decision problem from the published literature. A total of 23 economic evaluation studies were identified, including 9 with cost-effectiveness analyses. No economic evaluations of nivolumab in combination with ipilimumab in the treatment of MPM were identified from the review. Table 24 summarises the published economic evaluations that were deemed relevant to the submission. Appendix H presents the full results of published economic evaluations that were included in the SLR along with details of the search strategy and study selection process.

Table 24. Summary list of published cost-effectiveness studies

Author	Country	Publication type	Title
Cordony et al.[88]	UK	Journal article	Cost-effectiveness of pemetrexed plus cisplatin: malignant pleural mesothelioma treatment in UK clinical practice
Woods et al.[89]	UK	Journal article	Raltitrexed plus cisplatin is cost-effective compared with pemetrexed plus cisplatin in patients with malignant pleural mesothelioma
Rintoul et al.[90]	UK	Journal article	Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): An open-label, randomised, controlled trial
Stewart et al.[91]	UK	Journal article	Evaluating quality of life and cost implications of prophylactic radiotherapy in mesothelioma: health economic analysis of the SMART trial
Zhan et al.[92]	China	Journal article	Cost-effectiveness analysis of additional bevacizumab to pemetrexed plus cisplatin for malignant pleural mesothelioma based on the MAPS trial
Malacan and Carlson[93]	US	Conference abstract	Cost-effectiveness analysis of addition of bevacizumab to a standard chemotherapy doublet (pemetrexed + cisplatin) in patients with malignant pleural mesothelioma
Kogut and Babcock[94]	US	Conference abstract	Estimating the potential cost effectiveness of maintenance therapy following chemotherapy for malignant mesothelioma
Chetty et al.[95]	Scotland	Conference abstract	economic impact of adopting pemetrexed plus cisplatin for malignant pleural mesothelioma into Scottish clinical practice
Davey et al.[96]	Australia	Conference abstract	Value-for-money of pemetrexed plus cisplatin versus cisplatin alone in the treatment of malignant pleural mesothelioma

UK = United Kingdom; US = United States.

B.3.2 Economic analysis

This section describes the de novo economic model developed for the submission and the rationale for the model development.

B.3.2.1 Patient population

The economic evaluation considers nivolumab + ipilimumab in the first-line treatment of adults with untreated unresectable MPM. This is consistent with the study population of CheckMate-743 and the decision problem presented in Section B.1.1.

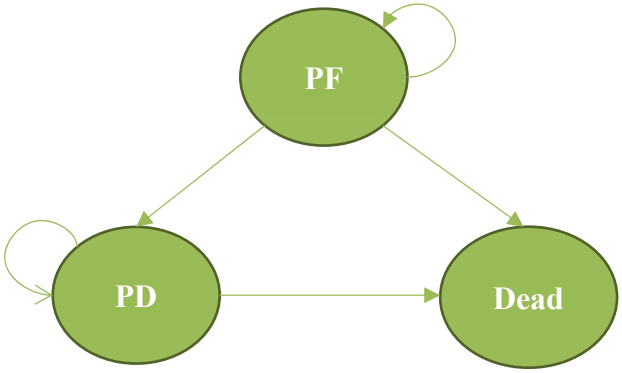
B.3.2.2 Model structure

A three health-state cohort-based partitioned survival model was developed to evaluate the incremental cost-effectiveness of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin in adults with previously untreated unresectable MPM.

The model was developed in Microsoft Excel and programmed using standard Excel functions where possible. Visual basic was used sparingly and was limited to running Monte-Carlo simulations in the probabilistic sensitivity analysis and for generating survival estimates. All model references and assumptions are clearly described within the Excel file.

Figure 24 presents the standard three health-state model structure. The model is composed of three key health states: progression free (PF), progressed disease (PD), and dead. The three health states represent the primary stages of disease in MPM: PF with first-line treatment, the occurrence of disease progression, and death. These health states correspond to the primary and secondary endpoints of the CheckMate-743 trial. This model structure is consistent with the approaches adopted in previous published economic evaluations within MPM and previous NICE technology appraisals of oncology products.[97]

Figure 24. Overview of the standard three health-state model

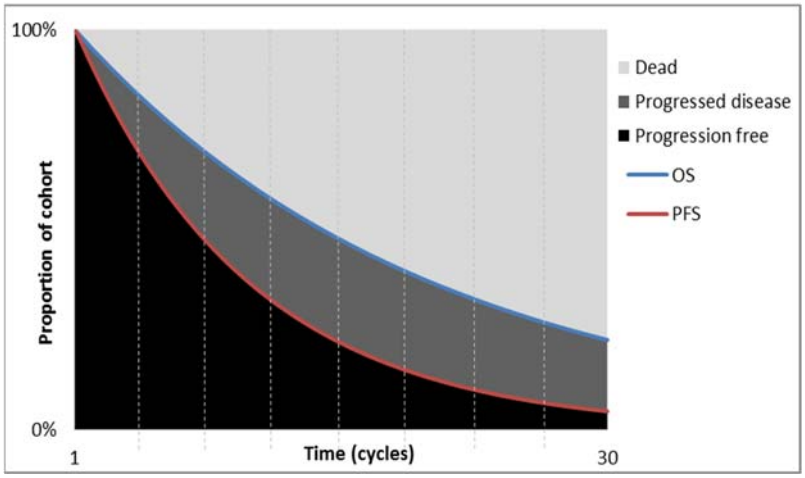


PD = progressed disease; PF = progression free.

Note: The partitioned survival model uses an area under the curve approach to estimate health-state occupancy.

Patients enter the model in the PF health state and first-line treatment. The number of patients in each health state is estimated using the partitioned survival method. The partitioned survival approach allows for modelling of OS and PFS based on study-observed events, which is expected to reflect disease progression and the long-term expected survival profile of patients. At the end of each cycle, the proportion of patients in PF, PD, and dead is calculated from parametric survival curves for PFS and OS estimated directly from the CheckMate-743 trial. The number of patients occupying each state in the model is derived directly from the cumulative survival probabilities of PFS and OS (area under the curve approach), with proportion of patients in the PD health state being calculated as the difference between OS and PFS. Figure 25 presents the partitioned survival method.

Figure 25. Overview of the partitioned survival method



OS = overall survival; PFS = progression-free survival.

The costs and effectiveness of treatments are calculated by combining the estimated time spent in the PF and PD states with the costs and health utilities assigned to those states. A 1-week cycle length is used to accommodate the administration cycles of the included therapies. The health care costs considered in the evaluation include the cost of drug acquisition, drug administration, monitoring, disease management, end of life care, management of AEs, and subsequent treatment. A 2-year treatment stopping rule is applied to the nivolumab + ipilimumab regimen, consistent with the CheckMate-743 clinical trial design. Pemetrexed + cisplatin or carboplatin was given for a maximum of 6 cycles or until disease progression, according to administration in the CheckMate-743 clinical trial. Table 25 summarises the core elements of the economic model.

Table 25. Features of the economic analysis

	Previous appraisal	Current appraisal	
Factor	**Pemetrexed disodium (TA181)**	**Chosen values**	**Justification**
Time horizon	29 months	20 years	Considered to be appropriate as the lifetime of patients with MPM accounting for typical age at diagnosis and advanced nature of disease.
Cycle length	3 weeks	1 week	Weekly cycles to accommodate differing administration cycles for therapies in the model.
Half-cycle correction	No	Yes	The model calculated mid-cycle estimates in each health state by taking the average of patients present at the beginning and at the end of each cycle.
Were health effects measured in QALYs? If not, what was used?	Yes	Yes	According to the NICE reference case.[98]

Factor	Previous appraisal Pemetrexed disodium (TA181)	Current appraisal Chosen values	Justification
Discount of 3.5% for utilities and costs	Outcomes were discounted at 3.5% but no discounting was applied to costs, as they were all incurred within 1 year.	Yes	According to the NICE reference case.[98]
NHS perspective?	Yes	Yes	According to the NICE reference case.[98]
Duration of treatment effect	Constant hazard ratio applied of model time horizon	Lifetime treatment effect of nivolumab + ipilimumab or pemetrexed + cisplatin or carboplatin	There is now long-term evidence of a robust and durable treatment effect lasting beyond discontinuation for immunotherapies.[99]
Source of utilities	EQ-5D and EQ-VAS individual patient-level data	CheckMate-743 EQ-5D individual patient data	According to the NICE reference case.[98]
Source of costs	Published literature, resource utilisation, and costs accepted in previous NICE submissions.	Published literature, resource utilisation, and costs accepted in previous NICE submissions.	These reflect resource utilisation and costs accepted in previous NICE submissions.[100]

MPM = malignant pleural mesothelioma; NHS = National Health Service; QALY = quality-adjusted life-year; VAS = visual analogue scale.

B.3.2.3 Intervention technology and comparators

The current analysis investigates the cost-effectiveness of nivolumab + ipilimumab compared with pemetrexed + cisplatin or carboplatin. Pemetrexed + cisplatin or carboplatin is considered the SOC therapy in the UK (see Section B.1.3.4) and is consistent with the comparator arm of the CheckMate-743 clinical trial.

B.3.3 Clinical parameters and variables

B.3.3.1 Methods for modelling survival

B.3.3.1.1 Data used for survival modelling

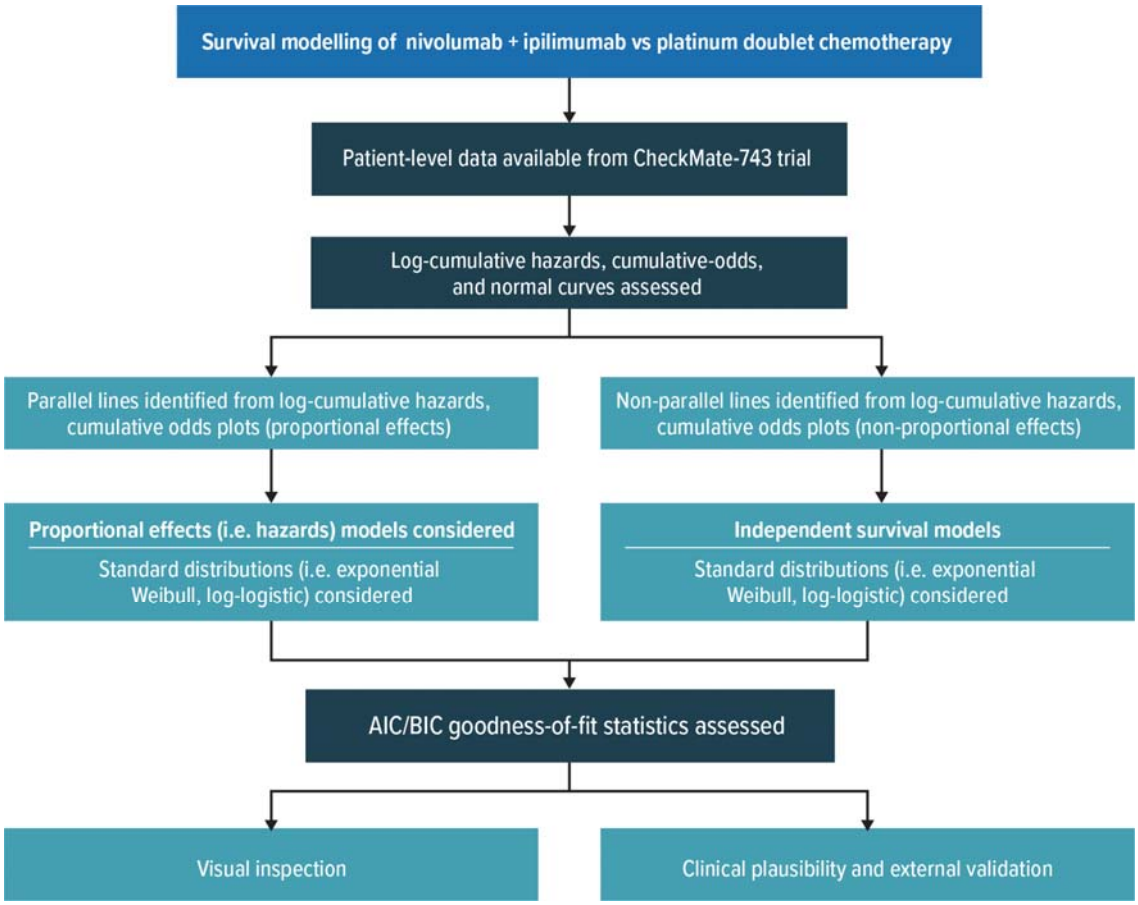
The primary data for the economic model are from the April 2020 database lock of CheckMate-743. At this point, the minimum follow-up for all patients was 22.1 months. This follow-up period is shorter than the required length of the economic analysis (a lifetime of up to 20 years), and 23% and 15% of patients were still alive at the end of the trial, with expected ongoing benefit from nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin, respectively. To estimate PFS and OS over the 20-year time horizon, parametric survival

curves were fitted to CheckMate-743 patient-level data and used to extrapolate survival beyond the study time horizon.

B.3.3.1.2 Process for fitting survival models

The process for fitting parametric survival curves to CheckMate-743 patient-level data was based on methods guidance from the Decision Support Unit at NICE.[101] Figure 26 presents the process for identifying the most appropriate parametric survival model for PFS and OS.

Figure 26. Identifying the parametric survival curves for the economic model



AIC = Akaike information criterion; BIC = Bayesian information criterion.

The steps required to determine the most appropriate parametric survival curves to use in the economic model included the following:

- Testing the proportional effects assumption: the log-cumulative hazards, log-cumulative odds, and standardised normal curve plots were assessed to determine if the data from CheckMate-743 indicate proportional effects. This assessment was done by testing the significance of the Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time and by visual inspection to determine if the survival curves of nivolumab + ipilimumab and PDC arms were parallel.
- In the event proportional effects held, a range of dependent parametric survival distributions were explored, with models fitted to both arms of CheckMate-743 simultaneously.

- When the proportional effects assumption did not hold, only independent survival models were assessed, in which survival models were fitted to each arm of the CheckMate-743 study independently.
- Within the various parametric survival distributions, the Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness-of-fit statistics were assessed to identify the best fitting survival models to the trial data.
- The final choice of parametric survival distributions used for the base-case model was based on the following:
  - The best fitting survival models by AIC and BIC statistics, which provide goodness of fit (compared with the KM data from CheckMate-743)
  - Visual fit of the extrapolations to the CheckMate-743 KM data
  - Clinical plausibility and external validation of the extrapolated survival estimates

It is important to consider goodness of fit because it measures the fit of the extrapolation against the trial data that are available. However, it is perhaps more important to consider the clinical plausibility of the extrapolated portion of the curve because it is the area with the highest uncertainty owing to lack of trial data.

B.3.3.1.3 External data used for selection and validation of overall survival

To validate the survival extrapolations against external data, data were sought that would be suitable for validation of both or either of the treatment arms from CheckMate-743. However, there is a paucity of long-term data relevant to the population for this assessment, and no suitable long-term registry data that could be used for validation were identified. Long-term data for NSCLC were identified and considered for validation of the survival extrapolations. However, based on clinical expert opinion, it was believed that this would not be appropriate and lead to an overestimation of long-term survival in the mesothelioma population.

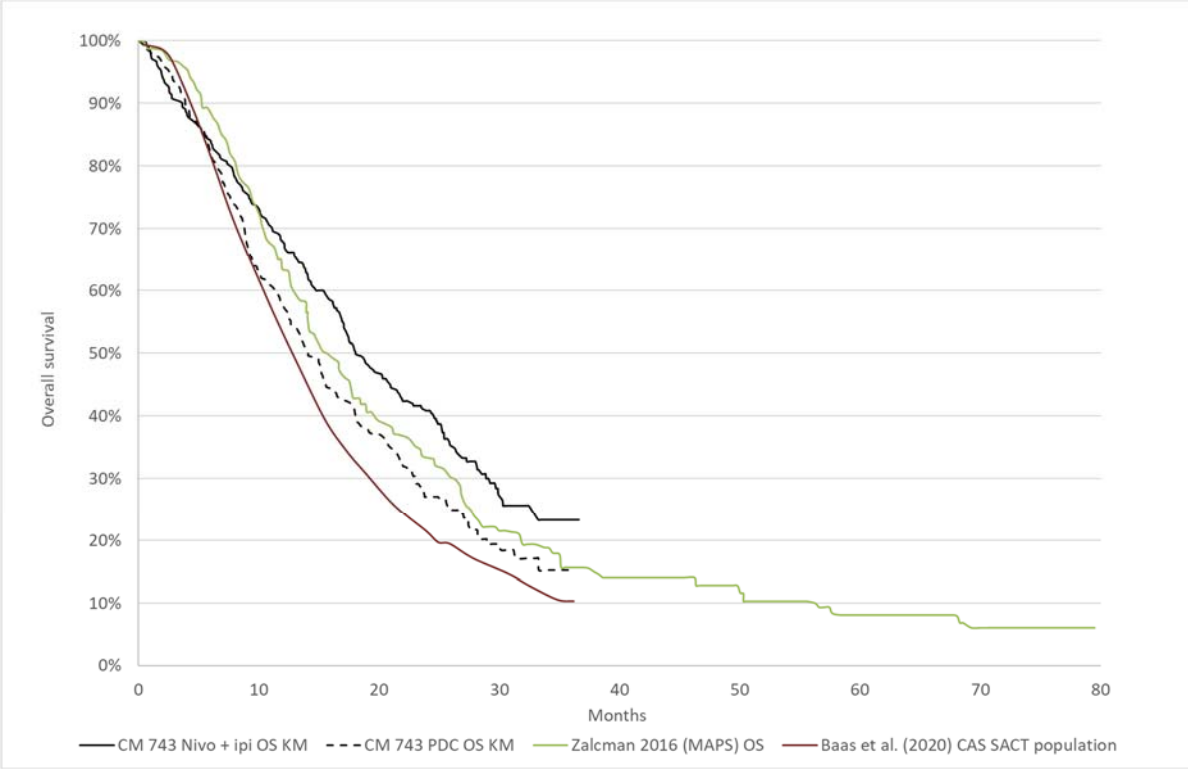
As reported in Section B.1.3.2, the National Mesothelioma Audit and CAS provide 3-year follow-up data for the UK. Although they provide potentially valuable information about expected survival within the current follow-up time of CheckMate-743 and more mature data, they do not provide much longer follow-up than CheckMate-743. However, as seen in Figure 27, digitised data for the SACT population of CAS indicate that the OS currently seen in the PDC arm of CheckMate-743 beyond the first year is higher than that in the SACT population from CAS.

External data providing longer follow-up than CheckMate-743 were identified from the study reported by Zalcman et al.[73] for the MAPS trial investigating bevacizumab + pemetrexed + cisplatin compared with pemetrexed + cisplatin for the treatment of patients with newly diagnosed unresectable MPM (see Section B.1.3.4.1). The reported results for this study provide follow-up data up to 80 months. The comparator arm of this trial, pemetrexed + cisplatin, is also aligned with the control arm of CheckMate-743 and, hence, provides a valuable source for external validation up to 80 months. Although it provides information on longer-term follow-up, the published data for the MAPS trial are not yet fully mature. As few patients remain at risk for the long-term survival outcome, the MAPS data are associated with uncertainty related to true long-term survival for patients with MPM. Absolute survival data

from the MAPS trial are not as informative for the validation of nivolumab + ipilimumab extrapolations as they are for the PDC extrapolations, given the difference in mechanisms of action and treatment effects compared with both interventions included in MAPS. However, given the superior results for nivolumab + ipilimumab compared with PDC observed in CheckMate-743, it would, at a minimum, be assumed that long-term predictions for nivolumab + ipilimumab would not result in worse survival than the PDC arm from MAPS.

Comparing the OS KM data from CheckMate-743 and the digitised KM OS data from the MAPS trial (Figure 27) shows that the PDC arm in the MAPS trial performs slightly better than the PDC arm in CheckMate-743. However, it appears that the trajectory of the survival curves is relatively aligned after 10 months. Thus, the PDC arm of MAPS was considered suitable to inform OS extrapolations for the PDC arm in CheckMate-743 in absolute terms as well as being able to inform the shape of the hazard function for the extrapolations. Of note, it can be observed from Figure 27 that, for both the PDC and nivolumab + ipilimumab arms, the current data cut for CheckMate-743 does not yet capture declining hazards that may be anticipated based on longer-term declining hazards in the MAPS trial. Thus, we anticipate that survival predictions based solely on fit to the current data cut for CheckMate-743 underpredict long-term survival.

Figure 27. MAPS and CheckMate-743 overall survival Kaplan-Meier data



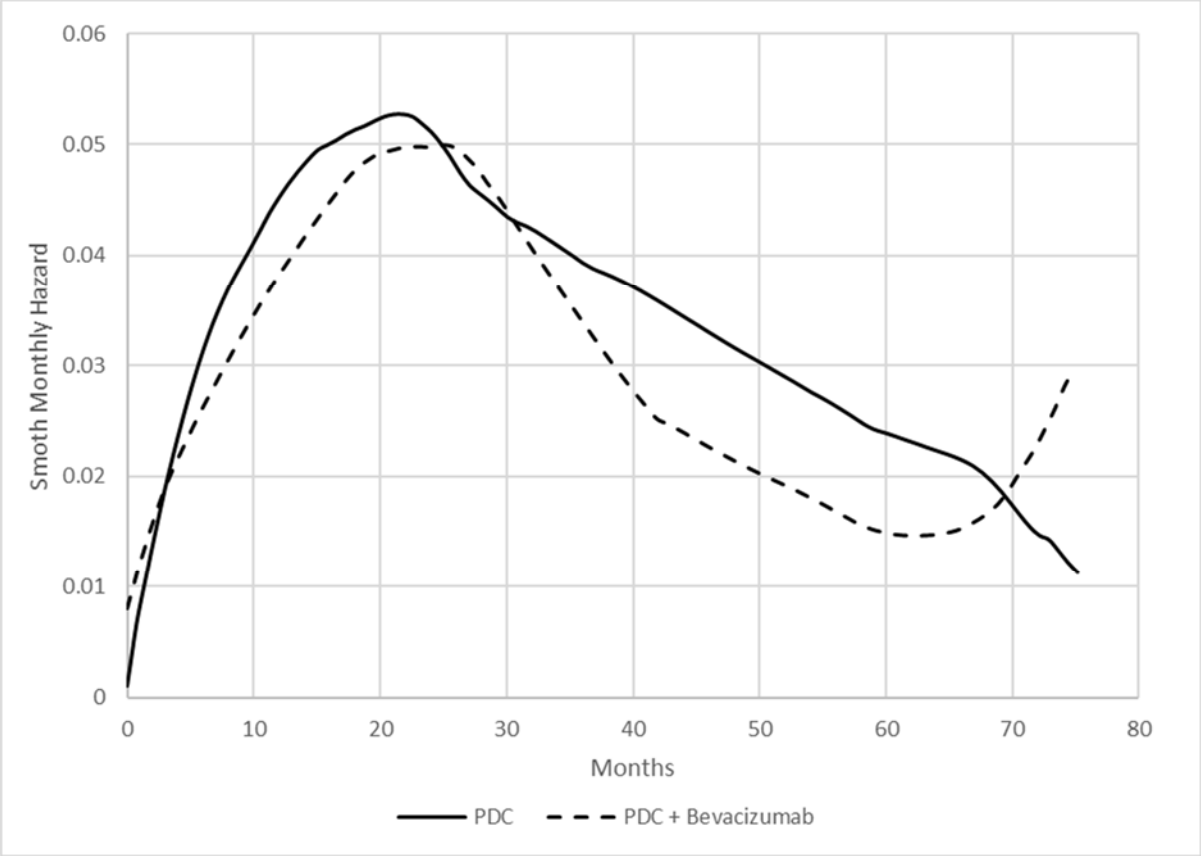
CAS = Cancer Analysis System; CM = CheckMate; KM = Kaplan-Meier; Nivo + ipi = nivolumab + ipilimumab; OS = overall survival; PDC = platinum-based doublet chemotherapy; SACT = systemic anticancer therapy.

Because of the development of a plateau in the longer-term follow-up of the MAPS data, the hazard function of the data was investigated so that it could guide the curve selection for CheckMate-743. To investigate the hazard shape of OS in the MAPS trial, pseudo patient-level data for both arms of MAPS were created following the methods proposed by Guyot et

al.[102] allowing survival analyses to be performed. This allowed us to explore the smooth hazard function (fitted with Muhaz package in R) for both arms of the MAPS trial as well as statistical distributions that would provide the best fit to the data. This means that information about underlying hazard function for a similar population could be used to inform the selection of the best fitting distributions for extrapolating the CheckMate-743 data.

As shown by the smoothed hazard for both the PDC and the PDC + bevacizumab arms in Figure 28, both curves follow a hazard function that initially increases before decreasing over time.

Figure 28. Smooth hazards for overall survival data for the PDC and PDC + bevacizumab arms of MAPS



PDC = platinum-based doublet chemotherapy.

Table 26 and Table 27 show that the survival analyses of the MAPS data indicate that the log-logistic distribution provides the best statistical fit to the data for both arms. Both AIC and BIC values are significantly lower for the log-logistic distribution: these can be considered the best fitting models based on [103] and the Raftery rule of thumb.[104] This also aligns with the log-logistic distribution's hazard function in which the hazard increases initially to a maximum before decreasing over time.[101] The other top fitting distributions for the PDC arm were log-normal and generalised gamma.

Table 26. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for the PDC arm of MAPS

Independent model	AIC rank	AIC	BIC
Log-logistic	1	1,446.87	1,453.70
Log-normal	2	1,455.84	1,462.67
Generalised gamma	3	1,456.06	1,466.31
Gamma	4	1,464.16	1,470.99
Weibull	5	1,472.68	1,479.52
Exponential	6	1,489.70	1,493.12
Gompertz	7	1,489.75	1,496.58

AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum-based doublet chemotherapy.

Table 27. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for the PDC + bevacizumab arm of MAPS

Independent model	AIC rank	AIC	BIC
Log-logistic	1	1,385.30	1,392.12
Generalised gamma	2	1,395.30	1,405.52
Gamma	3	1,396.57	1,403.38
Weibull	4	1,400.87	1,407.69
Log-normal	5	1,404.65	1,411.46
Exponential	6	1,410.87	1,414.28
Gompertz	7	1,412.05	1,418.87

AIC = Akaike information criterion; BIC = Bayesian information criterion; PDC = platinum-based doublet chemotherapy.

Based on the results from the survival analyses of the MAPS trial, the log-logistic distribution fits the data best. Further, as can be seen in Figure 27, it appears that there is a similar underlying hazard function for both treatment arms of MAPS. The hazard function of the trial follows a pattern with increasing hazards in the initial period before continuously decreasing over time. There is an increase in hazards from month 60 for the PDC + bevacizumab arm, but this is due to only two events occurring among the 8 patients at risk during this period. Given that a common hazard function is observed in both treatment arms, it could indicate a disease-specific hazard function, which would be important to consider in the heuristics for selecting the most appropriate survival distribution for extrapolation of CheckMate-743 data.

As noted earlier, although the MAPS data are likely to be the best available long-term external evidence, the reported data are still relatively immature with few patients at risk beyond 40 months. Thus, UK clinical experts were consulted on the expected survival with current treatments for this patient population. The clinical input received indicated that 5-year survival would be expected at 5%, 7.5-year survival at 2%, and 10-year survival at 0-2%. Thus, the clinicians indicated that the current observed survival for PDC in the MAPS trial is anticipated to be slightly higher than what would be expected for patients with MPM in the UK currently.

Heuristics for selection of survival extrapolation for overall survival based on external validation

Based on the information presented for validating against external data, the following key heuristics regarding long-term predictions and external validation were applied for selection of the most appropriate survival extrapolations of CheckMate-743 data:

- PDC arm
  - Survival predictions should result in long-term survival probabilities that continue to be slightly below the observed survival from the MAPS study.
  - The hazard function of the selected distribution should have an initial increase in hazards followed by long-term decreasing hazards.
- Nivolumab + ipilimumab
  - Survival predictions should result in survival probabilities better than the survival observed in both arms of the MAPS study.
  - The hazard function of the selected distribution should have an initial increase in hazards followed by long-term decreasing hazards.

B.3.3.1.4 External data used for selection and validation of progression-free survival

Compared with OS, there is less uncertainty regarding the extrapolation of PFS given that the PFS data are more mature, especially for the PDC arm. As with OS, the MAPS data were considered to be an appropriate source for external validation of the PDC arm. However, with the low proportion of patients in PFS at the end of both the CheckMate-743 and MAPS trial periods, the MAPS data provide limited additional validation over fit to the trial data. As it has been shown previously that PFS for immunotherapies does not follow the same pattern as for other oncology treatments,[105] the MAPS data were not considered appropriate for the nivolumab + ipilimumab arm. Therefore, selection of PFS distributions was primarily guided by statistical and visual fit to the CheckMate-743 data for both treatment arms.

B.3.3.2 Survival analysis

All survival modelling was conducted using the FlexSurv package in R and modelled using the FlexSurvReg function. Parametric survival models were fitted to individual patient-level data from the CheckMate-743 trial. For each endpoint, seven parametric models were considered for the extrapolation of “all-comers” patient-level data (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma, and generalised gamma). The following parameters were modelled:

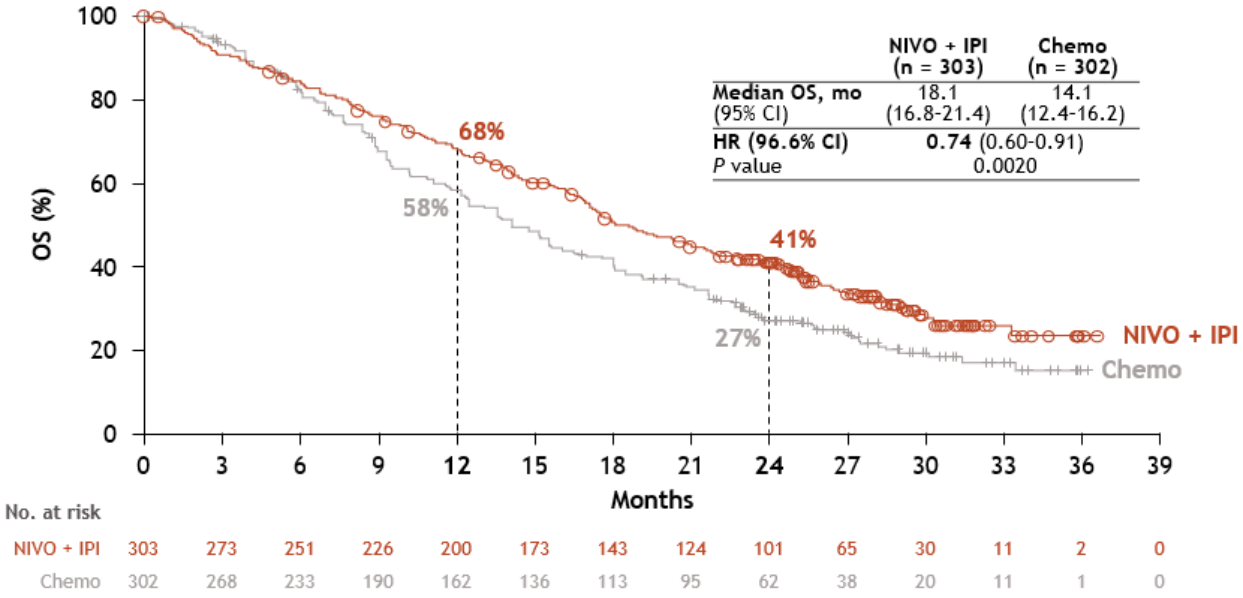
- Overall survival (see Section B.3.3.3)
  - Used to estimate proportion of patients alive at each cycle of the model and in the PD health state
- Progression-free survival (see Section B.3.3.4)
  - Used to calculate proportion of patients in the PF and PD health state

The following sections provide details of the survival models for each of these parameters.

B.3.3.3 Overall survival

Figure 29 shows the OS KM curves for nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin.

Figure 29. CheckMate-743: Kaplan-Meier plot of overall survival (all randomised patients)



CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival.

Notes: Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm and 41% in the chemo arm; subsequent immunotherapy was received by 3% and 20%, and subsequent chemotherapy by 43% and 32%, respectively.

Chemo in figure refers to platinum-based doublet chemotherapy.

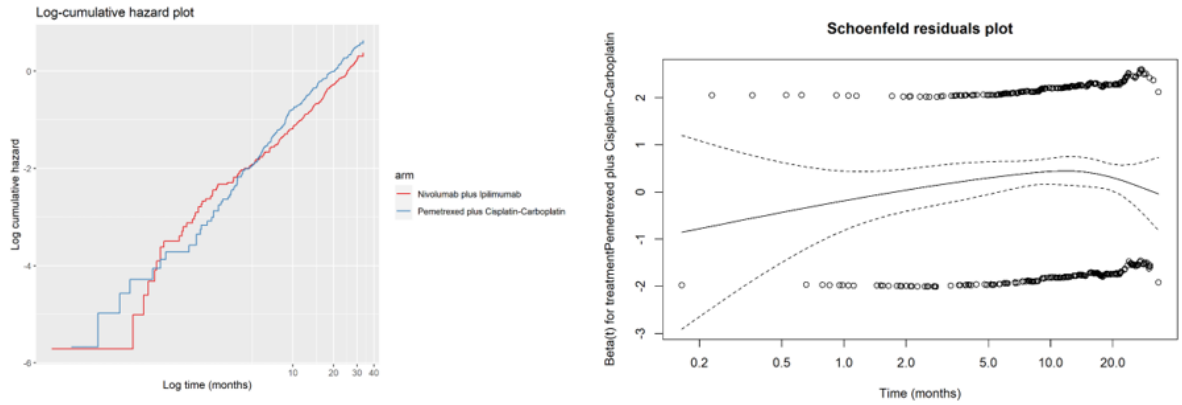
Source: Baas[18]

B.3.3.3.1 Testing of proportional hazards assumption

Visual inspection of the log-cumulative hazards and Schoenfeld residuals plots was undertaken to assess proportionality of treatment effects over time. A Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time failed to reject the proportional hazards assumption at a 5% significance level (P = 0.34). Visual inspection of the Schoenfeld residuals plot demonstrates a relatively but not completely linear pattern (Figure 30). However, inspection of the log-cumulative hazards plot reveals that the cumulative hazard for nivolumab + ipilimumab and PDC crosses at multiple time points, which could be seen, per definition, to falsify the assumption of proportional hazards. Further, the non-proportionality between immunotherapy and chemotherapy could also be seen to be clinically justified, as agreed by the company and the Evidence Review Group (ERG) to NICE's appraisal of atezolizumab in NSCLC (TA584).[106] Non-proportionality is clinically justified because immunotherapy has a different mechanism of action compared with chemotherapy, resulting in a delayed but more sustained survival benefit. Non-proportionality has also been demonstrated in several other previous immunotherapy appraisals in NSCLC (TA531, TA428, TA484, and TA584).[87,100,106,107] Based on this, it was decided that non-proportionality was the most plausible assumption for the current analyses. However, for completeness, both

independent and dependent survival models were fitted to the data with both options being available in the economic model.

Figure 30. Log-cumulative hazard plot and Schoenfeld residuals plot for nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin for overall survival



B.3.3.3.2 Assessing goodness-of-fit of parametric survival models within the trial period

Independent models

Nivolumab + ipilimumab

Table 28 summarises the goodness-of-fit statistics for independent survival models fitted to the OS endpoint of nivolumab + ipilimumab. As shown, several of the models have AIC values with a difference of less than 4 to the distribution with the lowest AIC; these can be considered the best fitting models based on the Burnham and Anderson rule of thumb.[103]

Table 28. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for nivolumab + ipilimumab

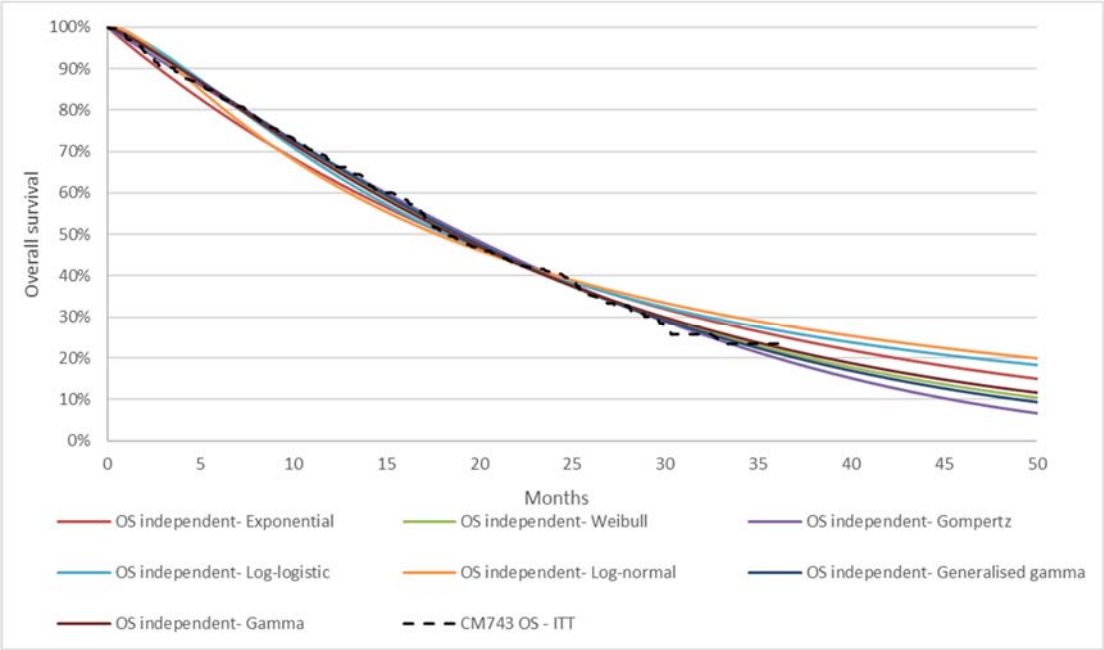
Independent model	AIC rank	AIC	BIC
Weibull	1	1,703.26	1,710.68
Gamma	2	1,703.74	1,711.17
Gompertz	3	1,704.14	1,711.57
Generalised gamma	4	1,705.11	1,716.25
Exponential	5	1,709.84	1,713.55
Log-logistic	6	1,710.87	1,718.3
Log-normal	7	1,720.36	1,727.79

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 31 shows the independent parametric models for nivolumab + ipilimumab compared with the CheckMate-743 KM data for OS. Visually, most of the curves fit the KM data well, apart from the log-normal, log-logistic, and exponential curves. The log-normal and

exponential models underestimate survival in the initial part of the KM curve, while all three overestimate survival towards the end of the KM data. The poorer fit to the clinical data aligns with the distributions ranking in terms of AIC and BIC values.

Figure 31. Independent parametric models overlaying the overall survival Kaplan-Meier data for nivolumab + ipilimumab



CM = CheckMate; ITT = intent to treat; OS = overall survival.

Table 29 presents the landmark OS for each distribution and the CheckMate-743 trial. The exponential, log-logistic, and log-normal distributions appear to slightly underestimate the median survival compared with the KM data, whereas all others result in a slight overestimate.

Table 29. Landmark absolute overall survival analysis for independent parametric distributions fitted to nivolumab + ipilimumab

	Curve	Absolute survival (%)								
Data set	Start year	6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 15	Yr 20	Median (mos)
CheckMate-743	Kaplan-Meier	84.0	67.9	40.8	23.3	-	-	-	-	18.10
Nivolumab + ipilimumab extrapolation	Weibull	84.0	66.9	39.5	21.9	6.0	0.1	0.0	0.0	18.40
	Gamma	83.8	66.3	39.4	22.7	7.2	0.4	0.0	0.0	18.17
	Gompertz	83.3	67.5	40.1	20.1	2.4	0.0	0.0	0.0	18.86
	Generalised gamma	84.1	67.3	39.6	21.3	5.0	0.0	0.0	0.0	18.63
	Exponential	79.7	63.5	40.3	25.6	10.3	1.1	0.1	0.0	17.94
	Log-logistic	84.0	65.2	40.1	26.8	14.6	5.7	3.2	2.1	17.94
	Log-normal	81.3	62.6	40.4	28.3	16.1	6.0	2.9	1.7	17.48

mos = months; Yr = year.

Pemetrexed plus cisplatin or carboplatin

Table 30 summarises the goodness-of-fit statistics for independent survival models fitted to the OS endpoint of pemetrexed + cisplatin or carboplatin. As for the nivolumab + ipilimumab arm, the differences in AIC and BIC values suggest that some of the distributions (specifically Gompertz, log-normal, and exponential) have a poorer fit to the trial data than other distributions.

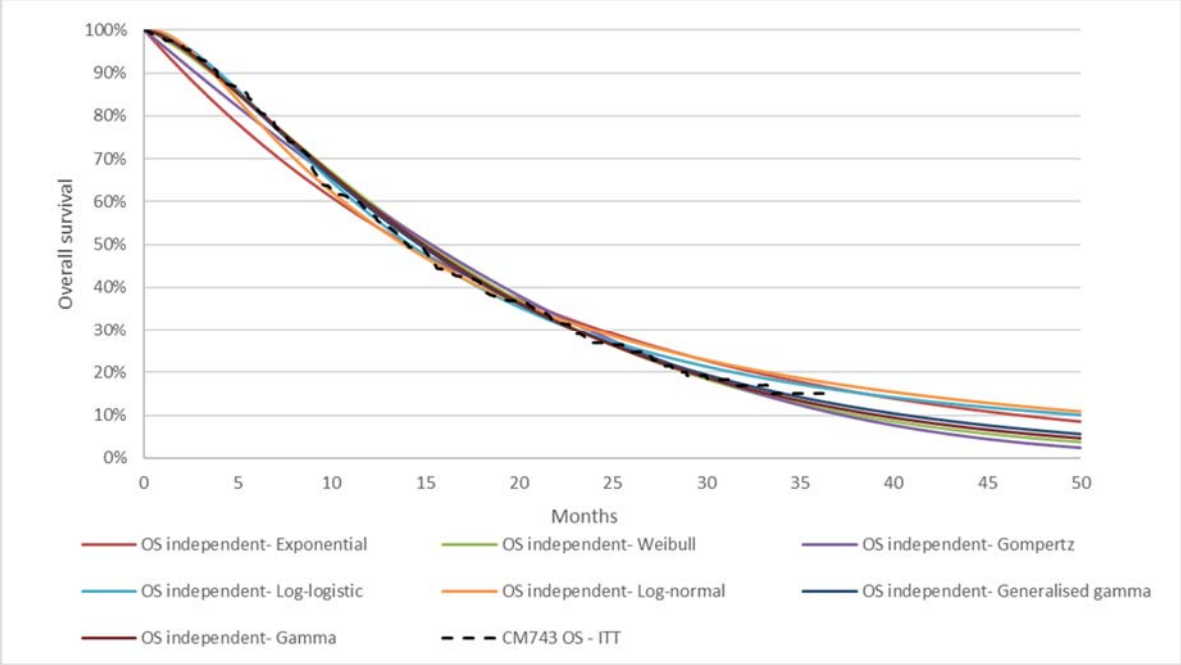
Table 30. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for pemetrexed + cisplatin or carboplatin

Independent model	AIC rank	AIC	BIC
Gamma	1	1,737.23	1,744.65
Log-logistic	2	1,737.31	1,744.73
Generalised gamma	3	1,738.71	1,749.84
Weibull	4	1,739.22	1,746.64
Gompertz	5	1,749.37	1,756.79
Log-normal	6	1,749.58	1,757.00
Exponential	7	1,756.98	1,760.69

AIC = Akaike information criterion; BIC = Bayesian information criterion.

This can also been confirmed with regards to visual fit in Figure 32 showing the independent parametric models for pemetrexed + cisplatin or carboplatin overlaid on the KM data from CheckMate-743 where these three distributions underestimate the initial part of the KM data. The exponential, log-logistic, and log-normal distributions also slightly overestimate survival at the end of the trial.

Figure 32. Independent parametric models overlaying the overall survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin



CM = CheckMate; ITT = intent to treat; OS = overall survival.

The landmark survival analysis presented in Table 31 shows that the distributions fitted to the PDC arm show a similar pattern to that of nivolumab + ipilimumab in that exponential, log-logistic and log-normal distributions appear to slightly underestimate the median survival compared with the KM data whereas all other curves result in a slight overestimate.

Table 31. Landmark absolute overall survival analysis for independent parametric distributions fitted to pemetrexed + cisplatin or carboplatin

	Curve	Absolute survival (%)								
Data set	Start year	6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 15	Yr 20	Median (mos)
CheckMate-743	Kaplan-Meier	82.2	57.7	27.0	15.2	-	-	-	-	14.10
Pemetrexed + cisplatin or carboplatin extrapolation	Gamma	81.6	59.4	28.2	12.5	2.2	0.0	0.0	0.0	14.49
	Log-logistic	81.7	57.3	28.6	16.5	7.5	2.4	1.2	0.7	13.80
	Generalised gamma	81.3	58.7	28.3	13.4	3.0	0.1	0.0	0.0	14.26
	Weibull	81.4	60.1	28.4	11.8	1.5	0.0	0.0	0.0	14.72
	Gompertz	78.7	59.6	29.5	11.3	0.5	0.0	0.0	0.0	14.95
	Log-normal	79.0	55.6	30.0	18.0	8.0	1.9	0.7	0.3	13.57
	Exponential	74.4	55.4	30.6	17.0	5.1	0.3	0.0	0.0	13.57

Mos = months; Yr = year.

B.3.3.3.3 Selection of base-case distributions

As presented earlier, several of the distributions had a statistical fit (AIC/BIC) that was considered within the assumption of similar fit to the underlying data. However, as shown in

Figure 33 and Figure 34, only log-logistic and log-normal presented a hazard function for both arms in line with the hazard function identified from analyses of the data from the MAPS trial. For the PDC arm, generalised gamma also provided a declining hazard over time, although not as marked a decline as for log-logistic and log-normal. All other distributions had constant or increasing hazards over time.

Figure 33. Nivolumab + ipilimumab independent parametric hazard function

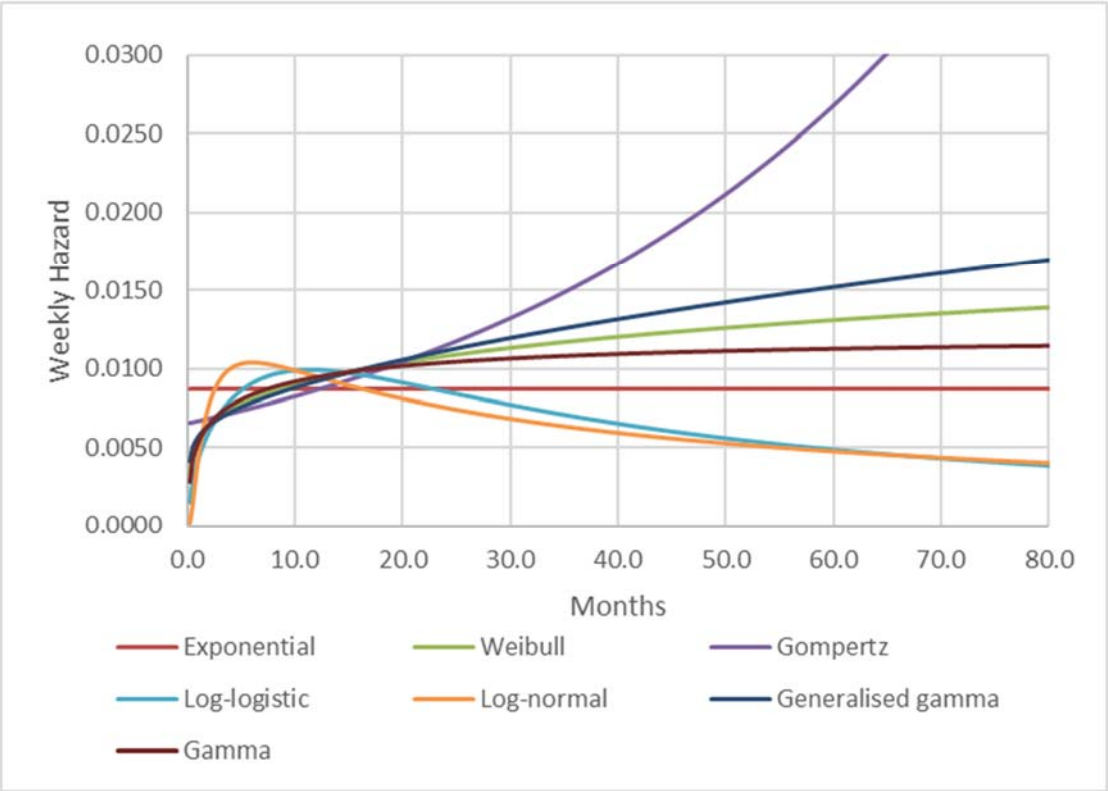
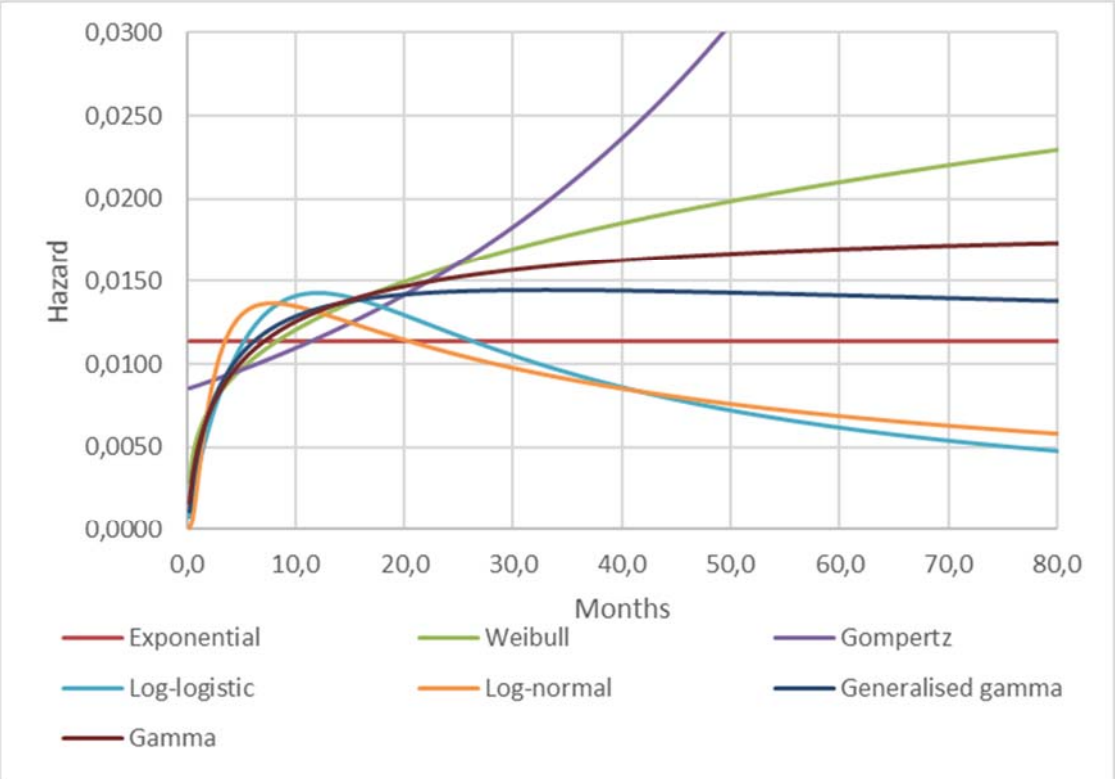


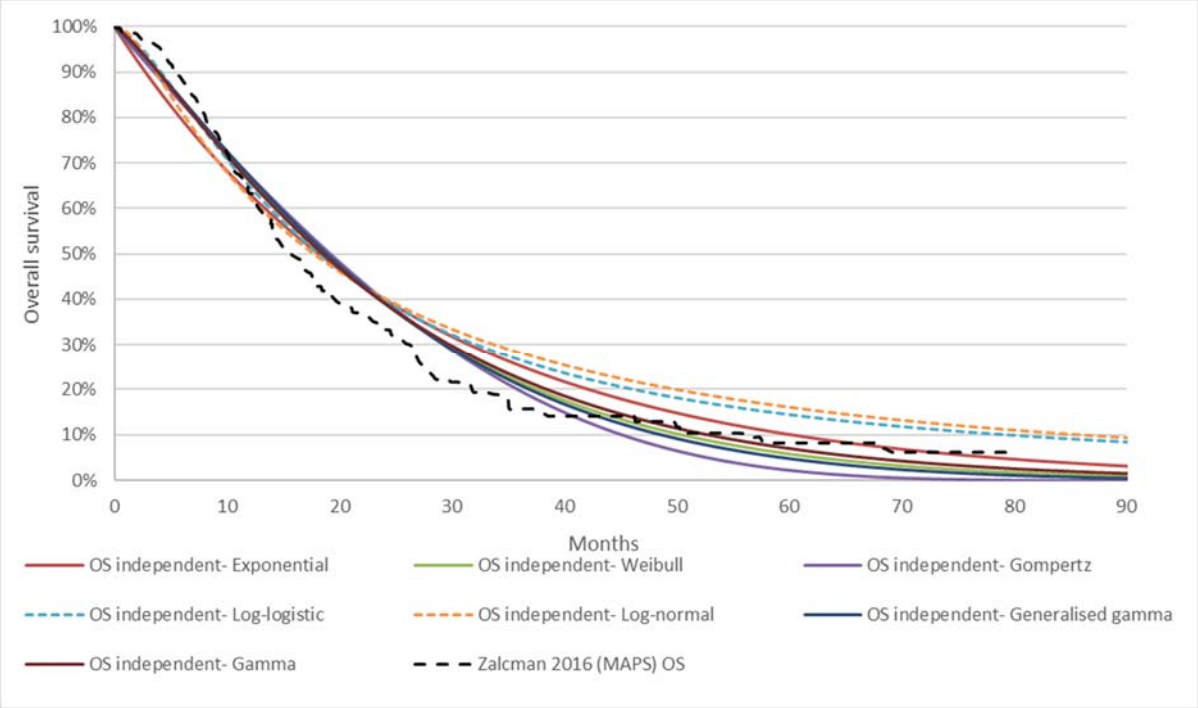
Figure 34. PDC independent parametric hazard function



PDC = platinum-based doublet chemotherapy.

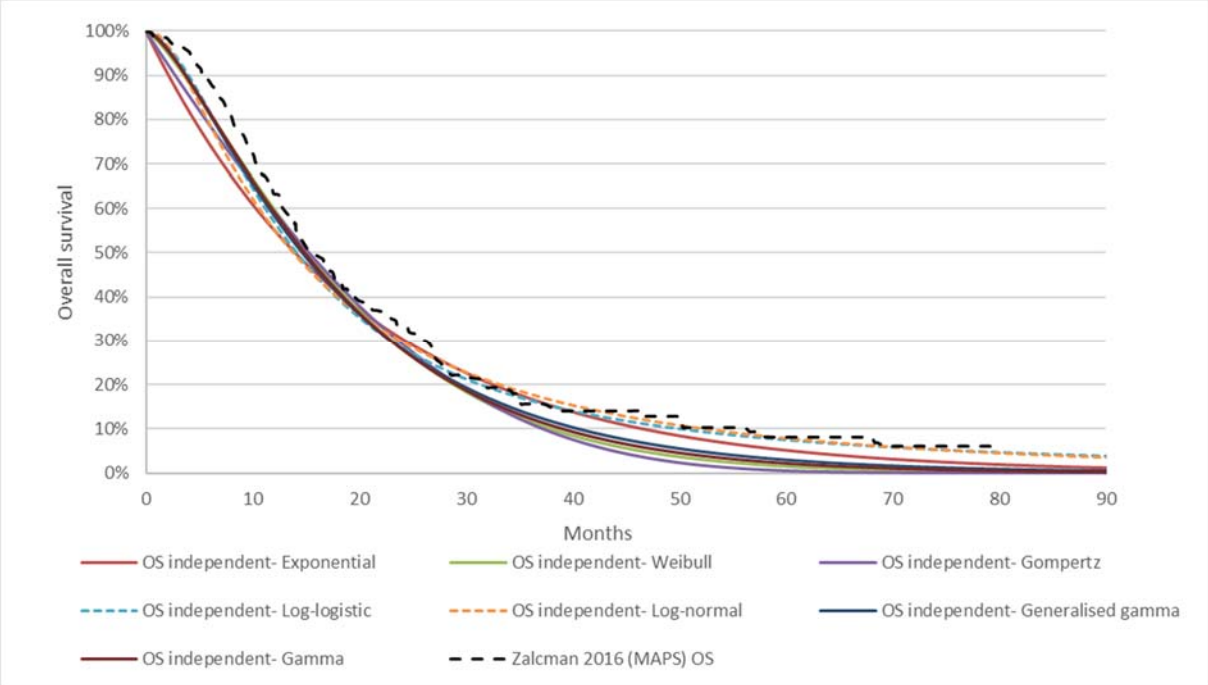
The deviation in hazard function for most of the distributions fitted to the CheckMate-743 data also result in the absolute survival not fulfilling the criteria of being slightly below the survival from MAPS for the PDC arm, and not lower survival than that observed in the MAPS trial for the nivolumab + ipilimumab arm (Figure 35 and Figure 36).

Figure 35. Independent parametric models overlaying the MAPS Kaplan-Meier data for nivolumab + ipilimumab



OS = overall survival.

Figure 36. Independent parametric models overlaying the MAPS Kaplan-Meier data for PDC



OS = overall survival; PDC = platinum-based doublet chemotherapy.

Table 32 summarises the final overall assessment of fit for all distributions as follows:

- Based on the Burnham and Anderson rule of thumb,[103] it was considered that a difference in AIC less than 4 with respect to the lowest AIC was appropriate, between 4 and 10 was neutral, and more than 10 was inappropriate in line with previous ERG arguments in a NICE assessment of cancer treatments.[108]
- Based on the Raftery rule of thumb,[104] it was considered that a difference in BIC more than 10 with respect to the BIC for distribution with the lowest BIC was inappropriate.
- Distributions with increasing hazard rates at the start and decline long-term were considered appropriate; hazard rates declining from the beginning were considered neutral; the remaining distributions were considered inappropriate.
- Based on clinical input, distributions with predicted survival for PDC slightly below the survival observed in MAPS are appropriate; predictions aligned with the MAPS data were considered neutral, and predictions above or significantly below survival in MAPS were considered inappropriate. For nivolumab + ipilimumab, predicted survival that is lower than that observed for PDC in MAPS was considered inappropriate.
- Overestimation and underestimation of median survival is provided for reference only and not used as a selection criterion, as it is considered to be accounted for via the AIC and BIC.

Table 32. Summary of assessment of selection criteria for distributions

Distribution	Distribution	AIC	BIC	Over/underestimates of median survival	Appropriate hazard function	Plausible survival predictions
Nivolumab + ipilimumab extrapolation	Weibull	✓	✓	↑	✗	✗
	Gamma	✓	✓	↑	✗	✗
	Gompertz	✓	✓	↑	✗	✗
	Generalised gamma	✓	✓	↑	✗	✗
	Exponential	-	✓	↓	✗	✗
	Log-logistic	-	✓	↓	✓	✓
	Log-normal	✗	✗	↓	✓	✓
Pemetrexed + cisplatin or carboplatin	Weibull	✓	✓	↑	✗	✗
	Gamma	✓	✓	↑	✗	✗
	Gompertz	✗	✗	↑	✗	✗
	Generalised gamma	✓	✓	↑	-[a]	-
	Exponential	✗	✗	↓	✗	✓
	Log-logistic	✓	✓	↓	✓	-
	Log-normal	✗	✗	↓	✓	✗

AIC = Akaike information criterion; BIC = Bayesian information criterion.

[a] The generalised gamma distribution has been marked as neutral, although it has an increasing hazard initially with long-term declining hazards because the long-term decline in hazards is less pronounced than would be expected from the MAPS data.

Based on the overall assessment presented in Table 32, the log-logistic distribution appears to be the most appropriate distribution for the nivolumab + ipilimumab arm. Although the AIC deviated slightly more than 4 from the best fitting curve, it is not deemed inappropriate for any of the other criteria. The only other distribution not leading to inappropriate long-term survival predictions for nivolumab + ipilimumab was the log-normal. This distribution had a poorer fit to the trial data but had an appropriate hazard function and slightly more optimistic long-term survival than the log-logistic distribution. Given that all other distributions except for log-logistic and log-normal resulted in implausible long-term predictions (key function of the extrapolations), none of those were considered potential candidates for nivolumab + ipilimumab.

For PDC, Weibull, gamma, and Gompertz distributions were seen to result in implausibly low survival predictions. Log-normal was considered implausibly high because it overpredicted the survival in MAPS, which has higher survival within the CheckMate-743 trial period. Thus, only generalised gamma, exponential, and log-logistic provided extrapolations that were not seen as implausible. However, the log-logistic distribution provided survival estimates that seem to be on the very upper bound of plausibility for the PDC arm, tracking the MAPS data closely. In contrast, the generalised gamma results in what could be considered low survival compared with the MAPS data. This was also confirmed in discussions with one of the clinical experts consulted in preparation for this submission, who stated that the log-logistic would probably be too optimistic, whereas the generalised gamma would be too pessimistic (see Appendix N). However, both log-logistic and generalised gamma did exhibit a hazard function in line with the smooth hazards observed from the MAPS trial and had good statistical fit to the trial data. The only intermediate distribution with regards to survival between log-logistic and generalised gamma is the exponential. However, the exponential distribution had a poor statistical and visual fit to the data and did not exhibit an appropriate hazard function.

Based on the overall assessment of the survival analyses, it is clear that extrapolation based on the current immature data cut is associated with uncertainties. In light of the mechanisms of action for immunotherapies, in which a long-term plateau in survival is anticipated, it is likely that that current extrapolations of the nivolumab + ipilimumab arm risk underpredicting long-term survival. As noted previously, a decrease in hazards over time, similar to that seen in the MAPS data, is yet to be fully observed in CheckMate-743 and would be anticipated to be more pronounced for nivolumab + ipilimumab than PDC owing to the aforementioned mechanism of action. This is supported by a much more pronounced plateau of the PFS curve observed in the nivolumab + ipilimumab arm compared with the PDC arm. Therefore, a long-term, durable OS benefit for patients treated with nivolumab + ipilimumab is anticipated to be confirmed when long-term OS data are available. This issue was clearly seen in the NICE appraisals of nivolumab for previously treated squamous and non-squamous NSCLC,[86,87] in which the initial extrapolations that were deemed optimistic by the ERG were, in fact, found to be pessimistic when more evidence was available during the CDF exit review. However, based on the currently available evidence, the log-logistic distribution appears to be the distribution with the overall best combination of fit and long-term extrapolation and, thus, was conservatively selected as the base case for nivolumab + ipilimumab. The slightly more optimistic survival predictions of log-normal were tested in a scenario.

Even for the PDC arm, the analyses show that there is considerable uncertainty regarding the selection of appropriate survival function. Although exponential has poor fit to the within-trial data, it provides the most plausible long-term extrapolation well aligned with the clinical expert input received. Therefore, it was selected as the base-case distribution instead of the log-logistic and generalised gamma. However, to overcome the poor fit to the trial data, the exponential distribution was used in a piecewise approach in combination with the KM data from the trial. In this approach, the trial data were used up to a break point followed by the long-term exponential extrapolation accounting for the uncertainty when events are fewer and the KM data more uncertain.

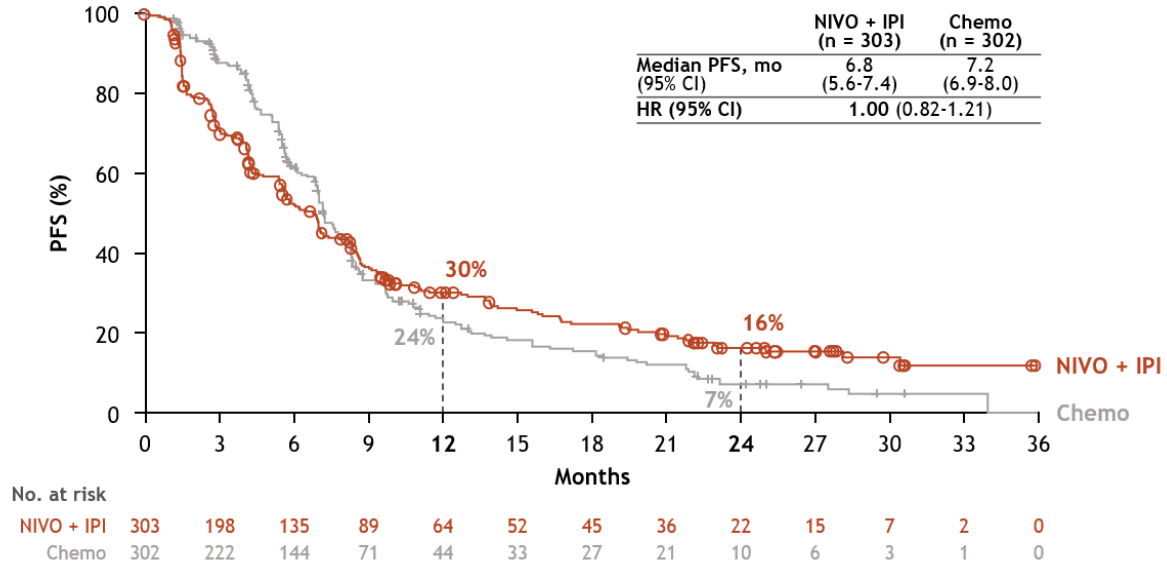
For the base-case analysis, this break point was set to 22 months. This was the approximate minimum patient follow-up at the database lock of CheckMate-743, and most censoring in the OS data in both treatment arms occurred after this point (see Figure 12). Bagust and Beale[109] warn of the risk of bias that can be introduced by censoring patients. Further, Latimer[110] highlights that the selection of a time point for switching from the KM curve to extrapolation becomes increasingly arbitrary as the effective sample size decreases. Therefore, selecting a time point before substantial censoring occurs maintains a suitable sample size from which to apply the extrapolation. However, the model also was set up to allow for testing of the impact of selecting an alternative break point.

Generalised gamma and log-logistic distributions were tested in scenario analyses, although considered to be too pessimistic and optimistic, respectively, regarding PDC survival.

B.3.3.4 Progression-free survival

Figure 37 presents the KM curves for PFS in the nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin arms.

Figure 37. CheckMate-743: Kaplan-Meier plot of progression-free survival by blinded independent central review (all randomised patients)



CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PFS = progression-free survival.

Notes: Per adapted mRECIST for pleural mesothelioma lesions and/or RECIST v1.1 for non-pleural lesions.

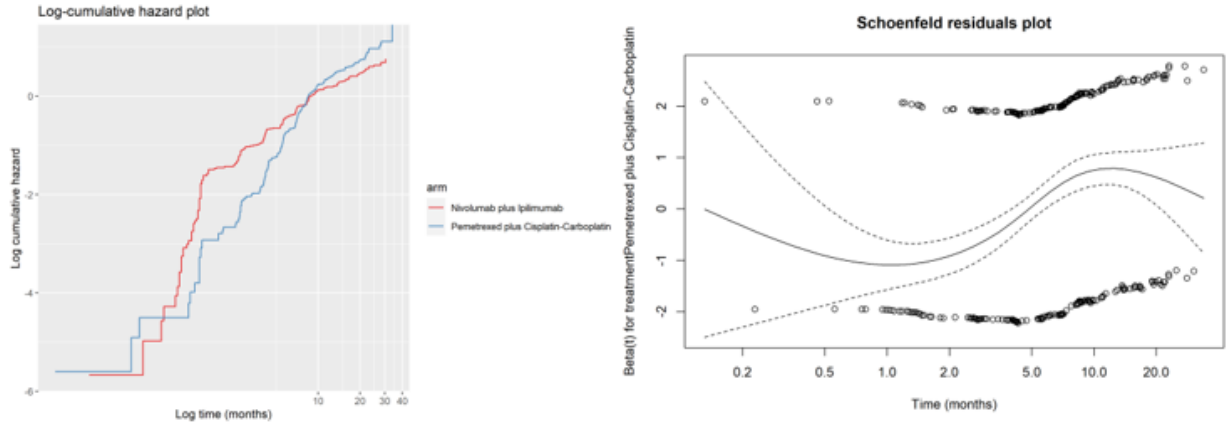
Chemo in figure refers to platinum-based doublet chemotherapy.

Source: Baas[18]

B.3.3.4.1 Testing of proportional hazards assumption

Visual inspection of the log-cumulative hazards and Schoenfeld residuals plots was undertaken to assess proportionality of treatment effects over time. Visually, it would appear the proportional hazards assumption does not hold given the non-linearity and crossover seen in the log-cumulative plot (Figure 38). A Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time use confirmed the rejection of the null hypothesis of proportional hazards ($P < 0.001$). Therefore, only independent parametric curves were considered appropriate for modelling PFS and are reported here. However, as for OS and completeness, both independent and dependent survival models were fitted to the data incorporated for selection in the economic model.

Figure 38. Log-cumulative hazard plot and Schoenfeld residuals plot for nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin



B.3.3.4.2 Assessing goodness of fit of parametric survival models

Table 33 provides a summary of the AIC and BIC goodness-of-fit statistics reported for the parametric distributions of the independent survival models for PFS fitted to the nivolumab + ipilimumab arm of CheckMate-743. As shown in Table 33, there were large differences in AIC and BIC between the best fitting distribution and most other distributions, indicating that several of the distributions would have a poor fit to the trial data. In fact, none of the distributions were within the difference in AIC (< 4 from the best fitting distribution) proposed by Burnham and Anderson[103].

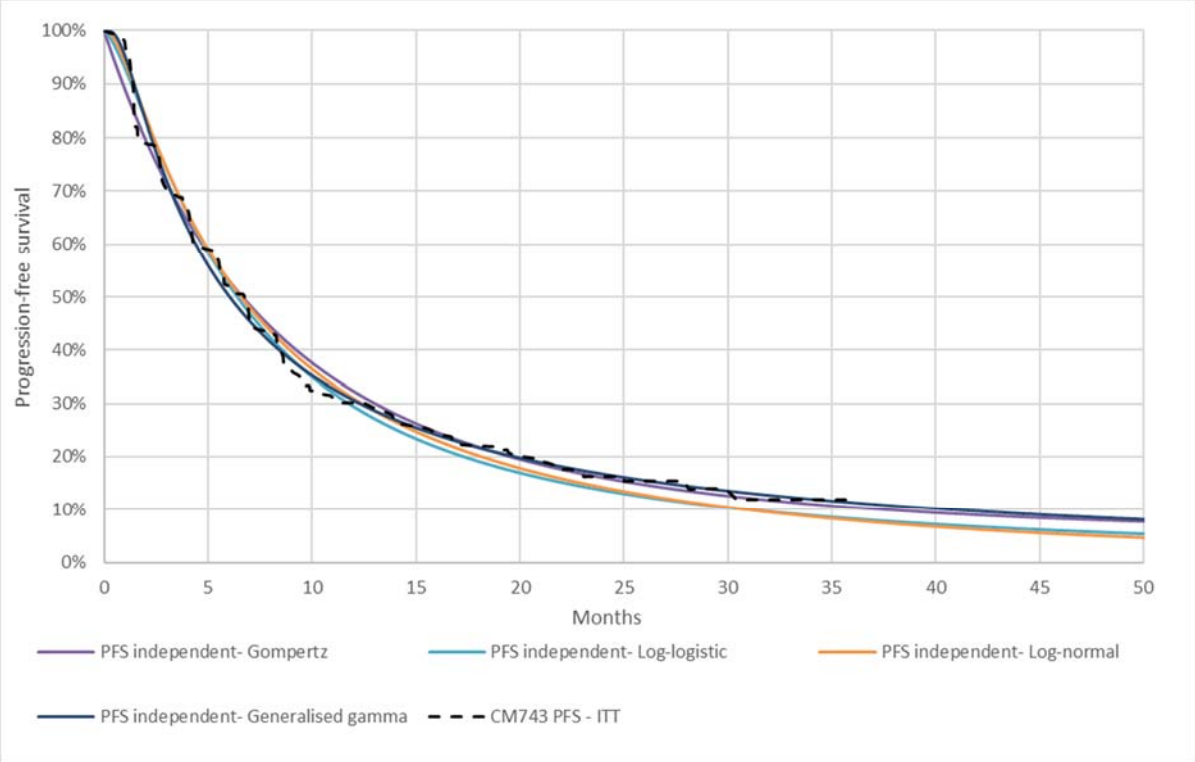
Table 33. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for nivolumab + ipilimumab

Arm	Distribution	AIC ranked	AIC	BIC
Nivolumab + ipilimumab	Generalised gamma	1	1,446.96	1,458.10
	Log-normal	2	1,453.04	1,460.46
	Log-logistic	3	1,461.66	1,469.09
	Gompertz	4	1,479.02	1,486.45
	Exponential	5	1,491.68	1,495.40
	Weibull	6	1,492.67	1,500.10
	Gamma	7	1,493.68	1,501.10

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Owing to the large difference in AIC and BIC, Figure 39 only shows the four independent parametric models for nivolumab + ipilimumab with the best AIC and BIC overlaid on the KM data from CheckMate-743 to aid comparison. As shown in Figure 39, the curves fit the trial period reasonably well until month 15 after which log-normal and log-logistic curves appear to underpredict the trial data. In line with the best AIC and BIC, the generalised gamma provides the best overall visual fit to the trial data followed by Gompertz.

Figure 39. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for nivolumab + ipilimumab



CM = CheckMate; ITT = intent to treat; PFS = progression-free survival.

The landmark PFS analysis presented in Table 34 shows that the Gompertz curve has the most optimistic long-term extrapolation. The Gompertz extrapolation appears to be too optimistic in the long-term, with absolute PFS remaining almost constant from year 10 to year 20. Thus, based on the statistical and visual fit to the data and plausibility of the extrapolation, the generalised gamma distribution was selected as the best fitting distribution to use for PFS for nivolumab + ipilimumab.

Table 34. Landmark absolute progression-free survival analysis for independent parametric distributions fitted to nivolumab + ipilimumab

	Curve	Absolute survival (%)								
Data set	Start year	6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 15	Yr 20	Median (mos)
CheckMate-743	Kaplan-Meier	52.1	30.2	16.3	11.9	—	—	—	—	6.80
Nivolumab + ipilimumab extrapolation	Generalised gamma	50.4	30.7	16.8	11.4	6.7	3.2	2.0	1.4	5.75
	Log-normal	53.2	31.0	14.2	8.0	3.3	0.8	0.3	0.1	6.21
	Log-logistic	52.4	29.6	13.8	8.3	4.3	1.7	1.0	0.6	5.98
	Gompertz	53.2	32.4	16.1	10.4	6.7	5.2	5.1	5.1	6.21
	Exponential	58.7	34.4	11.8	4.1	0.5	0.0	0.0	0.0	7.36
	Weibull	57.5	34.4	12.7	4.8	0.7	0.0	0.0	0.0	7.13
	Gamma	58.7	34.4	11.8	4.0	0.5	0.0	0.0	0.0	7.36

Mos = Months; Yr = Year.

Table 35 shows the goodness-of-fit statistics for the independent parametric distributions according to AIC/BIC criteria for the pemetrexed + cisplatin or carboplatin arm of CheckMate-743. As for nivolumab + ipilimumab, there were large differences in AIC and BIC between the best fitting distribution and most other distributions, indicating that several of the distributions would have a poor fit to the trial data.

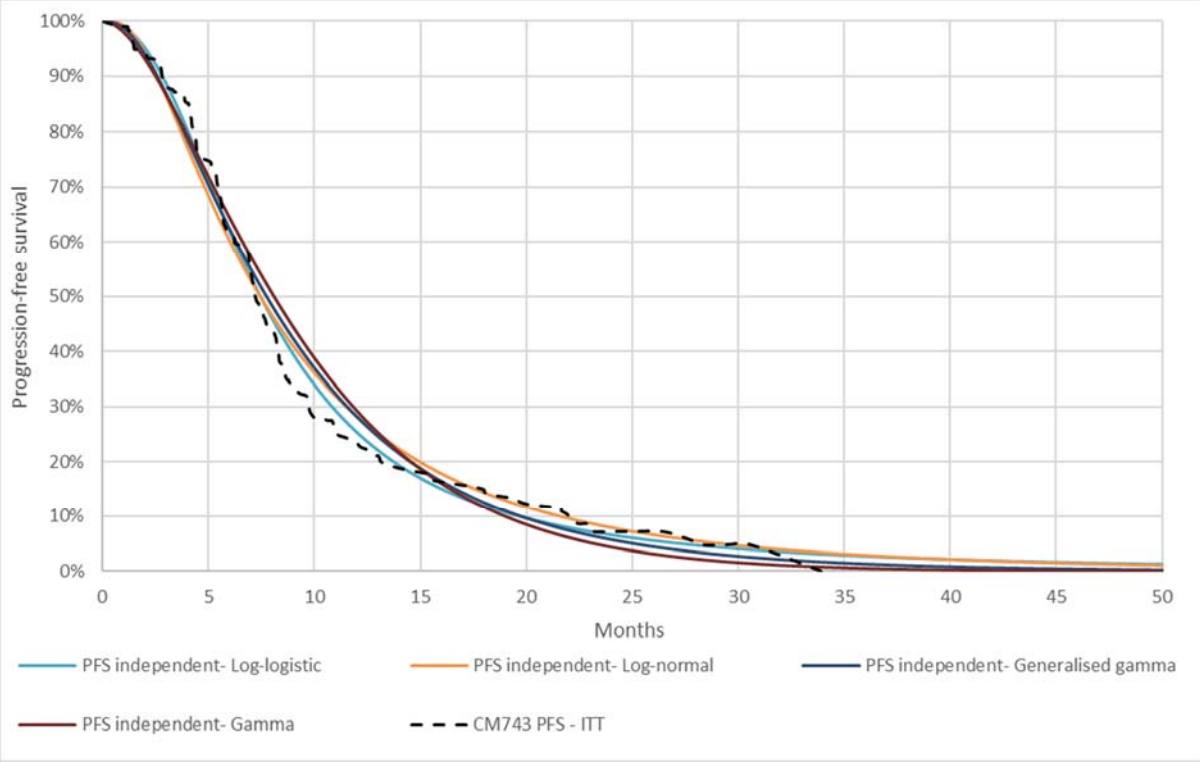
Table 35. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for pemetrexed + cisplatin or carboplatin

Independent model	AIC rank	AIC	BIC
Log-logistic	1	1,336.30	1,343.73
Generalised gamma	2	1,349.79	1,360.92
Gamma	3	1,353.93	1,361.35
Log-normal	4	1,355.49	1,362.91
Weibull	5	1,365.31	1,372.73
Gompertz	6	1,393.66	1,401.08
Exponential	7	1,400.95	1,404.66

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 40 shows the independent parametric models with best statistical fit to the data for pemetrexed + cisplatin or carboplatin compared with the KM data from CheckMate-743. None of the distributions fully capture the middle part of the KM curve, but the log-logistic fits slightly better than the other distributions. Log-logistic and log-normal both appear to fit the tail of the KM curve better than the other distributions.

Figure 40. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin



CM = CheckMate; ITT = intent to treat; PFS = progression-free survival.

Table 36 presents the landmark survival analysis. The table shows that log-logistic would result in the most optimistic long-term PFS extrapolation for PDC and therefore also could be seen as a conservative assumption in comparison to nivolumab + ipilimumab. Thus, log-logistic was selected as the best fitting distribution for PDC.

Table 36. Landmark absolute progression-free survival analysis for independent parametric distributions fitted to pemetrexed + cisplatin or carboplatin

	Curve	Absolute survival (%)								
Data Set	Start year	6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 15	Yr 20	Median (mos)
CheckMate-743	Kaplan-Meier	61.9	23.8	7.2	0.0	-	-	-	-	7.10
Pemetrexed + cisplatin or carboplatin extrapolation	Log-logistic	62.1	25.6	6.7	2.8	0.9	0.2	0.1	0.0	7.13
	Generalised gamma	62.5	28.4	5.8	1.4	0.1	0.0	0.0	0.0	7.36
	Gamma	64.5	29.4	4.5	0.6	0.0	0.0	0.0	0.0	7.82
	Log-normal	60.3	28.4	8.0	2.9	0.6	0.0	0.0	0.0	7.13
	Weibull	64.4	31.1	4.5	0.4	0.0	0.0	0.0	0.0	7.82
	Gompertz	60.5	32.9	6.5	0.6	0.0	0.0	0.0	0.0	7.59
	Exponential	56.4	31.8	10.1	3.2	0.3	0.0	0.0	0.0	6.90

Mos = months; Yr = year.

The independent generalised gamma curve is recommended as the base-case curve for nivolumab + ipilimumab while the independent log-logistic curve is recommended as the base-case curve for pemetrexed + cisplatin or carboplatin based on statistical fit, visual inspection, and clinical plausibility.

Additional adjustment and validation of the survival curves beyond the time of follow-up in the trials was also performed to ensure that the resulting survival estimates are plausible and externally valid. If PFS is greater than OS at any time, the PFS is assumed to be equivalent to OS to avoid a clinically implausible scenario.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

Health-related quality of life data were collected in CheckMate-743 using the EQ-5D-3L questionnaire (see Section B.2.6.1.5). Table 37 presents the EQ-5D-3L assessment schedule within the trial.

Table 37. EQ-5D-3L assessment schedule in CheckMate-743

On-study assessment	Follow-up assessment	Survival follow-up
0-12 weeks after initial dose Before each dose of nivolumab (Arm A) Before each dose of pemetrexed + cisplatin or carboplatin (Arm B)	Every 6 weeks for the first 12 months	Every 12 weeks thereafter until study discontinuation

Source: CheckMate-743[4]

Patient-level utility data from CheckMate-743 were used to derive progression-based utility values for the model. Analyses were conducted based on the prespecified patient-reported outcome statistical analysis plan using the trial data to derive utility values using UK-specific scoring algorithms.[78]

An analysis was conducted to assess model fit using utilities based on models with or without treatment. The analysis showed that treatment had a statistically significant impact on the utility values (P = 0.000). Therefore, treatment-specific utilities were selected for the model base-case analysis. Alternative non–treatment-specific utilities were tested in scenario analyses (see Section B.3.8.3). Table 38 presents the health-state utilities (overall and treatment specific).

Table 38. Overall and treatment-specific utilities by health state

		Treatment specific (SE)	
Utility approach	**Overall**	**Nivolumab + ipilimumab**	**Pemetrexed + cisplatin or carboplatin**
Health state			
Progression free	0.73 (0.01)	0.74 (0.01)	0.73 (0.01)
Progressed disease	0.62 (0.01)	0.65 (0.01)	0.58 (0.02)

SE = standard error.

Source: CheckMate-743[4]

B.3.4.2 Mapping

EQ-5D data were collected in CheckMate-743 in line with the NICE reference case. Utility values for health states and AEs for which CheckMate-743 data could not be used were obtained from the literature. Therefore, there was no need to use mapping techniques.

B.3.4.3 Health-related quality of life studies

An SLR was undertaken to identify HRQOL studies relevant to the decision problem from the published literature. The SLR was performed using the inclusion and exclusion criteria and the search strategy presented in Appendix I.

A total of 13 studies were identified that met the eligibility criteria for the review; however, none of the studies evaluated nivolumab + ipilimumab or used the EQ-5D in an appropriate population. Therefore, HRQOL data from CheckMate-743 were used in this submission.

B.3.4.4 Adverse reactions

The model included grade 3 or higher treatment-emergent AEs with at least 2% incidence. Treatment-related AEs with nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin, respectively, were derived from CheckMate-743. Table 39 presents the AE rates used in the economic model.

Table 39. Treatment-related adverse events ≥ grade 3 with an incidence ≥ 2%

Adverse event type	Nivolumab + ipilimumab	Pemetrexed + cisplatin or carboplatin
Neutropenia	0.7%	15.1%
Anaemia	0.3%	11.3%
Diarrhoea	3.3%	0.7%
Asthenia	0.0%	4.2%
Lipase increased	4.3%	0.4%
Thrombocytopenia	0.7%	3.5%
Nausea	0.3%	2.5%
Vomiting	0.0%	2.1%
Amylase increased	2.3%	0.0%
Leukopenia	0.0%	2.8%
Fatigue	1.0%	1.8%

Source: CheckMate-743[4]

Adverse event–related disutilities were obtained from the literature and are presented in Table 40. Disutility values were only applied when overall health-state utility values were selected (scenario analysis). When treatment-specific health-state utilities were applied, it was assumed that these already accounted for the disutility of AEs. Therefore, AE disutilities were set to 0 in the base-case analysis to avoid double counting.

A 1-week duration was used for all AEs except for asthenia, for which a 1-month duration was used. The durations were based on feedback from an oncologist.

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

Treatment-specific utilities by health state were selected for the model base-case analysis (Table 38). Alternative non–treatment-specific utilities were tested in a scenario analysis.

Table 40 summarises the disutilities assigned to AEs in the model. No publications reporting disutilities for AEs in MPM were identified; disutilities were derived from relevant publications in NSCLC. If no disutility value was available from the health technology assessment (HTA) submissions or other published literature, it was assumed that the disutility was 0. Disutility values were applied when overall utility values were selected in the scenario analysis. Disutility values were not applied when using treatment-specific utility values to avoid potential double counting because it was assumed that treatment-specific utilities account for the AEs experienced with each treatment.

Table 40. Disutility by adverse event (grade 3 and 4 adverse events with an incidence rate of ≥ 2%, for all treatments included in the analysis)

Adverse event	Disutility	SE	Reference
Neutropenia	0.090	0.015	Nafees et al.[111]
Anaemia	0.125	0.013	Lloyd et al.[112]
Diarrhoea	0.047	0.016	Nafees et al.[111]
Asthenia	0.073	0.018	Nafees et al.[111], assumed to be the same as fatigue
Lipase increased	0.000	0.000	Assumption
Thrombocytopenia	0.184	0.018	Attard et al.[113]
Nausea	0.048	0.016	Nafees et al.[111]
Vomiting	0.048	0.016	Nafees et al.[111]
Amylase increased	0.000	0.000	Assumption
Leukopenia	0.090	0.016	Nafees et al.[111], assumed the same as neutropenia

SE = standard error.

B.3.5 Cost and health care resource use identification, measurement, and valuation

The types of costs considered in the economic model include drug costs related to the intervention (see Section B.3.5.1), monitoring and management of the disease (see Section B.3.5.1.3), management of AEs (see Section B.3.5.4), and costs associated with subsequent therapy (see Section B.3.5.2).

An SLR was conducted to identify costs and resource use in the first-line treatment and ongoing management of patients with MPM as described in Appendix J.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

Table 41 provides a summary of the drug acquisition costs. These costs reflect the latest UK prices from the British National Formulary[114] and the Department of Health Drugs and pharmaceutical electronic market information tool (eMIT)[115] as of 3 June 2020. The cost per dose for each treatment is calculated by assuming no vial sharing (i.e., if the full vial is not used, the remaining content will be considered wastage). In addition, in the pemetrexed combination, 33% of patients were assumed to use cisplatin and 67% to use carboplatin, based on CheckMate-743.[4]

A flat nivolumab dosage of 360 mg every 3 weeks, aligning with the anticipated EMA licence,[16,17] is used in the base-case analysis. The model includes the option to use the weight-based dose of 3 mg/kg every 2 weeks that was used in CheckMate-743.[4] The weight-based dose is used in a scenario analysis.

There are simple PASs for nivolumab ([redacted]) and ipilimumab ([redacted]) approved by the Department of Health.

Table 41. Dosing details of included treatments

Drug	Tablet dose/ vial concentration	Pack size/vial volume	Cost per vial/pack, £	Dosage	Cost per dose, £	Source
Nivolumab	10 mg/mL	24 mL	2,633	360 mg Q3W, up to 2 years	3,950.00	British National Formulary[114]
		10 mL	1,097			
		4 mL	439			
Ipilimumab	5 mg/mL	40 mL	15,000	1 mg/kg Q6W, up to 2 years	7,500.00	British National Formulary[114]
		10 mL	3,750			
Pemetrexed[a]	25 mg/mL	20 mL	450	500 mg/m^2 Q3W for 6 treatment cycles	900.00	British National Formulary[114]
		4 mL	150			
Cisplatin	1 mg/mL	100 mL	6.66	75 mg/m^2 Q3W for 4 treatment cycles	5.68	Department of Health and Social Care[115]
		50 mL	4.12			
		10 mL	2.64			
Carboplatin	10 mg/mL	60 mL	28.22	550 mg/m^2 Q3W for 4 treatment cycles	23.72	Department of Health and Social Care[115]
		45 mL	27.90			
		15 mL	11.14			
		5 mL	3.75			

Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] In the pemetrexed combination, 33% of patients were assumed to use cisplatin and 67% carboplatin.

The duration of treatment in the model was based on the duration of treatment recorded in CheckMate-743. Given the minimum follow-up was 22.1 months in CheckMate-743 and that the maximum duration of treatment for the nivolumab + ipilimumab arm is 24 months,

complete duration of treatment data are available for the pemetrexed + cisplatin or carboplatin arm and data for 98.3% of patients are available for the nivolumab + ipilimumab arm.4 Thus, use of KM data for duration of treatment would be a viable option instead of parametric survival analyses. To investigate the potential of using parametric functions, survival analyses following the same methods as for PFS and OS (see Sections B.3.3.3 and B.3.3.4) were conducted (Appendix K). However, as demonstrated from those analyses, the parametric curves could not accurately reflect the treatment stopping rule for nivolumab + ipilimumab and do not reflect the treatment discontinuation that is displayed by the KM curve for pemetrexed + cisplatin or carboplatin. Therefore, it was decided that using data directly from CheckMate-743 would better represent the duration of treatment and thus was used in the model.

Two options to calculate treatment costs are included in the model. First, time-to-treatment discontinuation KM curves for nivolumab + ipilimumab and for pemetrexed + cisplatin or carboplatin from CheckMate-743 are used to calculate treatment costs based on the proportion of patients on treatment in each model cycle. The mean duration of treatment was [redacted] months for nivolumab + ipilimumab and [redacted] months for pemetrexed + cisplatin or carboplatin.[4] However, time-to-treatment discontinuation does not capture delayed or missed doses. The second approach uses the mean number of doses reported in CheckMate-743 to calculate treatment costs. The mean number of nivolumab doses received was [redacted] (adjusted from [redacted] to reflect three-weekly doses instead of two-weekly doses), and the mean number of ipilimumab doses received was [redacted][4] For the PDC arm, the mean number of doses received for pemetrexed, cisplatin, and carboplatin was [redacted], [redacted], and [redacted], respectively. Treatment costs were calculated using the mean number of doses and applied in the first model cycle. This was considered a conservative assumption because discounting was ignored for patients who receive nivolumab + ipilimumab in the second model-year.

The approach using the mean number of doses most accurately captures treatment costs because it accounts for delayed or missed doses and provides values for each treatment within the regimens. Therefore, this was chosen for the base-case analysis.

B.3.5.1.2 Drug administration costs

Table 42 presents the administration costs associated with all treatments. Nivolumab is administered every 3 weeks and ipilimumab every 6 weeks. The cost for delivering complex parenteral chemotherapy is applied when both treatments are administered. Whereas the cost for delivering simple parenteral chemotherapy is applied when nivolumab only is administered. Total administration costs are calculated using the mean number of doses from CheckMate-743 (see Section B.3.5.1.1).

Table 42. Administration cost per included treatment

Initial treatment	No. required	Source	Type of administration	Cost per administration, £	Source/comment
Nivolumab + ipilimumab	1	OPDIVO SmPC[116]; YERVOY SmPC[117]	Complex parenteral chemotherapy delivery: outpatient setting	259.08	NHS reference costs 2018/2019—SB13Z[117]. Deliver more complex parenteral chemotherapy at first attendance. Outpatient setting.
Nivolumab	1	OPDIVO SmPC[116];	Simple parenteral chemotherapy delivery: outpatient setting	183.54	NHS Reference Costs 2018/2019—SB12Z[117]. deliver simple parenteral chemotherapy at first attendance. Outpatient setting.
Pemetrexed + cisplatin or carboplatin	1	Alimta SmPC[62]; Carboplatin SmPC[72]; Cisplatin SmPC[71]	Complex parenteral chemotherapy delivery: outpatient setting	259.08	NHS reference costs 2018/2019—SB13Z[117]. Deliver more complex parenteral chemotherapy at first attendance. Outpatient setting.

NHS = National Health Service.

B.3.5.1.3 Monitoring costs

Table 43 presents the monitoring costs, which reflect treatment-specific resource use such as laboratory tests and scans that are required to ensure patients are tolerating the treatment well. These costs are both treatment specific and are required in addition to the disease management costs for patients in the PF health state outlined in Section B.3.5.3. Given that monitoring of treatment would be required not only when the patients receive each dose but as long as they stay on treatment, monitoring costs were applied based on the KM data for duration of treatment from CheckMate-743 rather than based on the mean number of doses. Monitoring costs were applied to the proportion of patients on treatment in each model cycle using separate KM curves for nivolumab + ipilimumab and for pemetrexed + cisplatin or carboplatin.

Table 43. Monitoring costs per included treatment

Monitoring cost	Frequency per week	Source	Unit cost, £	Source
Nivolumab + ipilimumab				
Outpatient visit	0.25	OPDIVO SmPC[116]; YERVOY SmPC[117]	194.17	NHS Improvement[118]: NHS reference costs 2018/2019. Consultant-led non-admitted face-to-face attendance, follow-up. WF01A. Medical oncology.

Monitoring cost	Frequency per week	Source	Unit cost, £	Source
Hepatic function test	0.25		1.10	NHS Improvement[118]: NHS reference costs 2018/2019. Clinical biochemistry (DAPS04).
Renal function	0.25		1.10	NHS Improvement[118]: NHS reference costs 2018/2019. Clinical biochemistry (DAPS04).
CBC	0.25		2.79	NHS Improvement[118]: NHS reference costs 2018/2019. Haematology (DAPS05).
Thyroid test	0.25		2.15	NICE NG145[118] (Thyroid disease: assessment and management) Resource impact report —thyroid function test.
Total cost per 1 week (model cycle)			**£50.33**	
Pemetrexed + cisplatin or carboplatin				
Outpatient visit	0.25	Alimta SmPC[62]; Carboplatin SmPC[72]; Cisplatin SmPC[71]	194.17	NHS Improvement[118]: NHS reference costs 2018/2019. Consultant-led non-admitted face-to-face attendance, follow-up. WF01A. Medical oncology.
Hepatic function test	0.25		1.10	NHS Improvement[118]: NHS reference costs 2018/2019. Clinical biochemistry (DAPS04).
Renal function	0.25		1.10	NHS Improvement[118]: NHS reference costs 2018/2019. Clinical biochemistry (DAPS04).
CBC	0.33		2.79	NHS Improvement[118]: NHS reference costs 2018/2019. Haematology (DAPS05).
Total cost per 1 week (model cycle)			**£50.02**	

CBC = complete blood cell count; NHS = National Health Service.

B.3.5.2 Subsequent treatment

On failure with first-line treatment of nivolumab + ipilimumab or pemetrexed + cisplatin or carboplatin (i.e., on entry to the PD health state), a proportion of the initial randomised cohort will go on to a subsequent treatment.

Patients are assumed to receive a subsequent SACT in the second line. Table 44 presents the distribution of subsequent therapies received by initial treatment and the duration of the subsequent therapies. The percentage of patients on each treatment is based on subsequent treatments as reported in CheckMate-743. Four subsequent treatment strategies were omitted because of low usage (< 1%). The median duration of second-line therapy in MPM (1.7 months) was assumed to be the same for all interventions, based on Waterhouse et al.[119]. Given that immunotherapies would be expected to have a longer duration of treatment compared with chemotherapies, the equal duration of second-line therapy should be considered a conservative assumption given the higher proportion of immunotherapies in the PDC arm. Thus, if data were available for each treatment's duration of treatment, the subsequent therapy cost for the PDC arm would likely be higher than assumed here.

Table 44. Distribution and duration of subsequent treatments applied in the base-case model

Subsequent treatment	Duration of treatment (months)	Percentage of patients	
		Nivolumab + ipilimumab	Pemetrexed + cisplatin or carboplatin
Nivolumab	1.7	2.2%	17.5%
Ipilimumab	1.7	0.6%	1.3%
Pembrolizumab	1.7	0.6%	7.3%
Bevacizumab	1.7	6.2%	3.4%
Carboplatin	1.7	27.7%	16.7%
Cisplatin	1.7	12.5%	3.4%
Pemetrexed	1.7	37.7%	20.5%
Gemcitabine	1.7	7.8%	19.2%
Vinorelbine	1.7	4.7%	10.7%

Sources: Bristol-Myers Squibb[4]; Waterhouse et al.[119]

Table 45 presents the acquisition cost of each subsequent treatment included.

Table 45. Dosing details of included treatments

Treatment	Tablet dose/vial concentration	Pack size/ vial volume	Cost per vial/ pack, £	Dosage	Cost per dose, £	Source
Nivolumab	10 mg/mL	24 mL	2,633	360 mg Q3W, up to 2 years	3,950.00	British National Formulary[114]
		10 mL	1,097			
		4 mL	439			
Ipilimumab	5 mg/mL	40 mL	15,000	1 mg/kg Q6W, up to 2 years	7,500.00	British National Formulary[114]
		10 mL	3,750			
Pembrolizumab	25 mg/mL	4 mL	2,630	200 mg/m2 Q3W for 6 treatment cycles	5,260.00	British National Formulary[114]
Bevacizumab	25 mg/mL	16 mL	902.70	8 mg/kg Q3W	1,354.04	British National Formulary[114]
		4 mL	225.67			
Carboplatin	10 mg/mL	60 mL	28.22	550 mg/m2 Q3W for 4 treatment cycles	35.40	Department of Health and Social Care[115]
		45 mL	27.90			
		15 mL	11.14			
		5 mL	3.75			
Cisplatin	1 mg/mL	100 mL	6.66	75 mg/m2 Q3W for 4 treatment cycles	17.22	Department of Health and Social Care[115]
		50 mL	4.12			
		10 mL	2.64			
Pemetrexed	1 mg	500 mg	450	500 mg/m2 Q3W	900.00	British National Formulary[114]
		100 mg	150			
Gemcitabine	100 mg/mL	20 mL	42.19	1,000 mg/m2 Q3W	55.31	Department of Health and Social Care[115]
		10 mL	13.09			
		2 mL	3.28			
Vinorelbine	10 mg/mL	5 mL	133.28 (10 vials)	25 mg/m2 every week	13.33	Department of Health and Social Care[115]
		1 mL	36.71 (10 vials)			

Q3W = every 3 weeks; Q6W = every 6 weeks.

Table 46 presents administration costs for each subsequent treatment included in the model.

Table 46. Administration costs of subsequent treatments

Treatment	Resource	Cost per administration, £	Units
Nivolumab	Simple parenteral chemotherapy delivery: outpatient setting	183.54	1.00
Ipilimumab		183.54	1.00
Pembrolizumab		183.54	1.00
Bevacizumab		183.54	1.00
Carboplatin		183.54	1.00
Cisplatin		183.54	1.00
Pemetrexed		183.54	1.00
Gemcitabine		183.54	1.00
Vinorelbine		183.54	1.00

Sources: OPDIVO SmPC[116]; YERVOY SmPC[117]; Alimta SmPC[62]; Carboplatin SmPC[72]; Cisplatin SmPC[71]; NHS Improvement[118]; NHS Reference Costs 2018/2019 - SB12Z. Deliver simple parenteral chemotherapy at first attendance. Outpatient setting.

B.3.5.3 Health-state unit costs and resource use

Table 47 and Table 48 present the disease management costs for patients in the PF and PD health states. The disease management costs are presented as resource use required every week to provide care to patients with unresectable MPM regardless of treatment.

Table 47. Disease management costs (progression-free health state)

Resource	No. required per week	Source (resource use)	Unit cost, £	Source
Outpatient visit	0.18	TA531	194.17	NHS reference costs 2018/2019. Consultant-led non-admitted face-to-face attendance, follow-up. WF01A. Medical oncology.
Chest radiography	0.13	TA531	27.82	NICE TA199 (£24.04 in 2009 inflated to 2018/2019 using the PSSRU HCHS/NHSCII).
CT scan (chest)	0.01	TA531	83.23	NHS reference costs 2018/2019. RD20A: computerised tomography scan of one area, without contrast, 19 years and over. Outpatient.
CT scan (other)	0.01	TA531	92.73	NHS reference costs 2018/2019. RD23Z: computerised tomography scan of two areas without contrast. Outpatient.
ECG	0.02	TA531	72.57	NHS reference costs 2018/2019. RD51A: simple echocardiogram, 19 years and over.
Total cost per 1 week			**£42.60**	

CT = computed tomography; ECG = electrocardiogram; HCHS = Hospital and Community Health Service; NHS = National Health Service; NHSCII = NHS Cost Inflation Index; PSSRU = Personal Social Services Research Unit.

Sources: NHS Improvement[118]; Curtis[120]; NICE[121]; NICE[100]

Table 48. Disease management costs (progressed disease health state)

Resource	No. required per week	Source (resource use)	Unit cost, £	Source
Outpatient visit	0.15	TA531	194.17	NHS reference costs 2018/2019. Consultant-led non-admitted face-to-face attendance, follow-up. WF01A. Medical oncology.
Chest radiography	0.13	TA531	27.82	NICE TA199 (£24.04 in 2009 inflated to 2018/2019 using the PSSRU HCHS/NHSCII).
CT scan (chest)	0.01	TA531	83.23	NHS reference costs 2018/2019. RD20A: computerised tomography scan of one area, without contrast, 19 years and over. Outpatient.
CT scan (other)	0.01	TA531	92.73	NHS reference costs 2018/2019. RD23Z: computerised tomography scan of two areas without contrast. Outpatient.
ECG	0.02	TA531	72.57	NHS reference costs 2017/2018. RD51A: simple echocardiogram, 19 years and over.
GP home visit	0.50	TA531	96.45	PSSRU 2015 pg 177-8; cost per home visit, including 11.4 minutes for consultations and 12 minutes for travel, inflated from TA531 to 2018/2019 using the PSSRU NHSCII.
Therapist visit	0.50	TA531	48.00	PSSRU 2019; pg 133; cost per hour for community occupational therapist (including training).
Total cost per 1 week			**£107.85**	

CT = computed tomography; ECG = electrocardiogram; GP = general practitioner; HCHS = Hospital and Community Health Services; NHS = National Health Service; NHSCII = NHS Cost Inflation Index; PSSRU = Personal Social Services Research Unit.

Sources:NHS Improvement[118]; Curtis[120]; NICE[121]; NICE[100]; Curtis[122]

Table 49 summarises the end of life/terminal care costs. End of life/terminal care costs are applied as a one-off cost to all patients who are newly entering the death state over the time horizon of the model.

Table 49. End of life/terminal care cost (one-off)

Resource	No. required per week	Source (resource use)	Unit cost, £	Source
Community nurse visit	7.56	TA531	64.00	PSSRU 2019; pg 117[120]; cost per hour Band 8A (including qualifications)
GP home visit	1.89	TA531	96.45	PSSRU 2015 pg 177-78[120]; cost per home visit, including 11.4 minutes for consultations and 12 minutes for travel, inflated from TA531 to 2018/2019 using the PSSRU NHSCII
Macmillan nurse	13.50	TA531	42.69	Assumed 66.7% of community nurse costs–per hour
Drugs and equipment	1.00	TA531	578.56	The value used in Brown et al., 2013[123] (Marie Curie report figure of 240 pounds inflated) and further inflated to 2018/2019 costs using PSSRU NHSCII—per patient
Terminal care in hospital	0.56	TA531	4,138.87	NHS reference costs 2018/2019 DZ17L, DZ17P, DZ17T: respiratory neoplasms without/with single/with multiple interventions - non-elective long stays and non-elective short stays; weighted sum of HRG codes by activity; assumed 0.92 number of excess days (Brown et al., 2013)[123]; 0.92 was multiplied with weighted sum of non-elective short stays and added to weighted sum of non-elective long stays
Terminal care in hospice	0.17	TA531	5,173.59	Assumed 25% increase on hospital inpatient care (Brown et al., 2013)[123]
Total cost (one-off)			**£5,018.27**	

GP = general practitioner; HRG = Health Care Resource Group; NHS = National Health Service; NHSCII = NHS Cost Inflation Index; PSSRU = Personal Social Services Research Unit.

Sources:NHS Improvement[118]; Curtis[120]; NICE[121]; NICE[100]; Curtis[122]; Brown et al.[123]

B.3.5.4 Adverse reaction unit costs and resource use

Table 50 presents the cost associated with individual AEs.

Table 50. Cost of treatment-related adverse events (grade ≥ 3 adverse events with an incidence rate of ≥ 2%, for all treatments included in the analysis)

Adverse event	Cost per episode, £	References
Neutropenia	1,251.42	Brown et al.[123] inflated to 2018/2019 using PSSRU HCHS inflation indices up to 2014/2015 then NHSCII indices thereafter[120]
Anaemia	2,795.95	TA531[100] inflated to 2018/2019 values from 2015/2016 values using PSSRU NHSCII[120]
Diarrhoea	1,032.62	Brown et al.[123] inflated to 2018/2019 using PSSRU HCHS inflation indices up to 2014/2015 then NHSCII indices thereafter[120]
Asthenia	2,953.19	Brown et al.[123] inflated to 2018/2019 using PSSRU HCHS inflation indices up to 2014/2015 then NHSCII indices thereafter[120]
Lipase increased	771.58	NICE TA451[124]; inflated to 2018/2019 using PSSRU HCHS inflation indices up to 2014/2015 then NHSCII indices thereafter[120]
Thrombocytopenia	125.63	TA531[100]; NICE ID865 inflated to 2018/2019 values from 2015/2016 values using PSSRU NHSCII[120]
Nausea	1,032.62	Brown et al.[123] inflated to 2018/2019 using PSSRU HCHS inflation indices up to 2014/2015 then NHSCII indices thereafter[120]
Vomiting	1,036.69	NICE TA531[100]; NICE TA192[125] inflated to 2018/2019 values from 2015/2016 values using PSSRU NHSCII[120]
Amylase increased	771.58	Assumed same as lipase increased
Leukopenia	1,251.42	Assumed same as neutropenia

HCHS = Hospital and Community Health Service; NHSCII = NHS Cost Inflation Index; PSSRU = Personal Social Services Research Unit.

Table 51 presents the total cost of AEs incorporating the cost of each AE and the proportion of patients incurring each AE for each included treatment.

Table 51. Total cost of adverse events per treatment

Treatment	Total cost of adverse events, £
Nivolumab + ipilimumab	106.13
Pemetrexed + cisplatin or carboplatin	726.23

The total cost of AEs is applied as a one-off in the first model cycle.

B.3.5.5 Miscellaneous unit costs and resource use

There are no additional costs included in the model except those outlined in the previous sections.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 52. Summary of variables applied in the economic model

Area	Variable	Value	Reference to section in submission
General	Patient population	Adults with unresectable MPM	Section B.3.2.1
	Time horizon	20 years	Section B.3.2.2
	Model cycle length	Weekly	
	Discount rate	3.5% for both costs and outcomes	
	Complex administration	£259.08	Section B.3.5.1
Acquisition costs	Nivolumab	£3,950.00 per dose	Section B.3.5.1
	Ipilimumab	£7,500.00 per dose	Section B.3.5.1
	Pemetrexed	£900.00 per dose	Section B.3.5.1
	Cisplatin	£5.68 per dose	Section B.3.5.1
	Carboplatin	£23.72 per dose	Section B.3.5.1
Subsequent treatment acquisition costs	Nivolumab	£3,950.00 per dose	Section B.3.5.1.3
	Ipilimumab	£7,500.00 per dose	Section B.3.5.1.3
	Pembrolizumab	£5,260.00 per dose	Section B.3.5.1.3
	Bevacizumab	£1,354.04 per dose	Section B.3.5.1.3
	Carboplatin	£35.40 per dose	Section B.3.5.1.3
	Cisplatin	£17.22 per dose	Section B.3.5.1.3
	Pemetrexed	£900.00 per dose	Section B.3.5.1.3
	Gemcitabine	£55.31 per dose	Section B.3.5.1.3
	Vinorelbine	£13.33 per dose	Section B.3.5.1.3
Monitoring costs	Nivolumab + ipilimumab	£50.33 per week	Section B.3.5.1.3
	Pemetrexed + cisplatin or carboplatin	£50.02 per week	Section B.3.5.1.3
Health-state costs	PF cost per week	£42.60	Section B.3.5.1.3
	PD cost per week	£107.85	Section B.3.5.1.3
End of life costs	Terminal care	£4,595.92	Section B.3.5.1.3
AE costs	Neutropenia	£1,251.42	Section B.3.5.4
	Anaemia	£2,795.95	Section B.3.5.4
	Diarrhoea	£1,032.62	Section B.3.5.4
	Asthenia	£2,953.19	Section B.3.5.4
	Lipase increased	£771.58	Section B.3.5.4
	Thrombocytopenia	£125.63	Section B.3.5.4
	Nausea	£1,032.62	Section B.3.5.4
	Vomiting	£1,036.69	Section B.3.5.4

Area	Variable	Value	Reference to section in submission
	Amylase increased	£771.58	Section B.3.5.4
	Leukopenia	£1,251.42	Section B.3.5.4
Health-state utilities	PF	0.73 (0.01)	Section B.3.5.4
	PD	0.62 (0.01)	Section B.3.5.4
AEs for nivolumab + ipilimumab	Neutropenia	0.7%	Section B.3.4.4
	Anaemia	0.3%	Section B.3.4.4
	Diarrhoea	3.3%	Section B.3.4.4
	Asthenia	0.0%	Section B.3.4.4
	Lipase increased	4.3%	Section B.3.4.4
	Thrombocytopenia	0.7%	Section B.3.4.4
	Nausea	0.3%	Section B.3.4.4
	Vomiting	0.0%	Section B.3.4.4
	Amylase increased	2.3%	Section B.3.4.4
	Leukopenia	0.0%	Section B.3.4.4
AEs for pemetrexed + cisplatin or carboplatin	Neutropenia	15.1%	Section B.3.4.4
	Anaemia	11.3%	Section B.3.4.4
	Diarrhoea	0.7%	Section B.3.4.4
	Asthenia	4.2%	Section B.3.4.4
	Lipase increased	0.4%	Section B.3.4.4
	Thrombocytopenia	3.5%	Section B.3.4.4
	Nausea	2.5%	Section B.3.4.4
	Vomiting	2.1%	Section B.3.4.4
	Amylase increased	0.0%	Section B.3.4.4
	Leukopenia	2.8%	Section B.3.4.4
Disutilities (SE)	Neutropenia	0.090 (0.015)	Section B.3.4.5
	Anaemia	0.125 (0.013)	Section B.3.4.5
	Diarrhoea	0.047 (0.016)	Section B.3.4.5
	Asthenia	0.073 (0.018)	Section B.3.4.5
	Lipase increased	0.000 (0.000)	Section B.3.4.5
	Thrombocytopenia	0.184 (0.018)	Section B.3.4.5
	Nausea	0.048 (0.016)	Section B.3.4.5
	Vomiting	0.048 (0.016)	Section B.3.4.5
	Amylase increased	0.000 (0.000)	Section B.3.4.5
	Leukopenia	0.090 (0.016)	Section B.3.4.5

AE = adverse event; MPM = malignant pleural mesothelioma; PD = progressed disease; PF = progression free; SE = standard error.

B.3.6.2 Assumptions

Table 53 summarises the key model assumptions and data gaps.

Table 53. Key assumptions within the economic model

Model inputs	Data gaps/assumption	Explanation
DoT	A 2-year maximum treatment duration is applied to nivolumab and ipilimumab. For nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin, mean doses are used to model treatment acquisition and administration costs, and KM DoT is used to model treatment monitoring costs.	In CheckMate-743, patients received immunotherapy for up to 24 months in the absence of disease progression or unacceptable toxicity.[4] The mean doses accurately reflect the number of doses of each treatment received in the clinical trial. The KM DoT curve accurately reflects the treatment duration in the clinical trial for both therapies (see Section B.3.5.1).
Subsequent treatment	Duration of subsequent treatments is based on the median DoT for patients with advanced MPM treated with second-line systemic therapy.[119]	As a large proportion of patients in the pemetrexed + cisplatin or carboplatin arm receive nivolumab as the subsequent treatment (which is an expensive immunotherapy assumed to be received for 1.7 months in subsequent treatment), the assumptions regarding DoT have an impact on the subsequent treatment costs. However, immunotherapy is expected to be more effective than second-line chemotherapies; the 1.7 month DoT for nivolumab may be a conservative assumption.
Disease management costs	It is assumed PF and PD costs are applied as a constant cost.	Disease management could make a significant contribution to the total incremental cost and is based on management of treatment-naive stage IV or recurrent NSCLC. Assuming these costs are constant is a simplified approach. There is insufficient evidence to amend this assumption
Compliance	The model assumes that compliance to treatment in CheckMate-743 is reflective of the real world.	Traditionally, compliance rates seen within clinical trials are higher than those seen in a real-world setting. However, the expected compliance of nivolumab + ipilimumab—and the impact this has on efficacy—is unknown at this point. Without further information, a 100% compliance rate is inherently assumed. That is, the efficacy seen within CheckMate-743 is assumed to be reflective of the real-world setting.

Model inputs	Data gaps/assumption	Explanation
AEs	It is assumed that all AEs are applied as a one-off cost in the first cycle of the model.	For AEs that do not occur within the first year or that are ongoing, their application in the model in the first cycle may overestimate costs and disutility owing to discounting.
Quality of life	The user can choose between applying overall or treatment-specific health-state utilities. Treatment-specific health-state utilities are included in the base-case analysis.	The utility values based on the EQ-5D-3L were derived from the CheckMate-743 using UK weights.

AE = adverse event; DoT = duration of treatment; KM = Kaplan-Meier; MPM = malignant pleural mesothelioma; NSCLC = non-small cell lung cancer; PD = progressed disease; PF = progression free; UK = United Kingdom.

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Table 54 presents total costs, life-years gained (LYGs), QALYs, and incremental costs per QALY for nivolumab + ipilimumab versus PDC. Compared with PDC, nivolumab + ipilimumab generated 0.702 incremental QALYs and 0.916 incremental LYGs, and the nivolumab + ipilimumab–treated cohort had higher total lifetime costs. The ICER was £77,502 per QALY gained. Disaggregated results are presented in Appendix L.

Table 54. Base-case incremental results of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin in first-line unresectable MPM

Technologies	Total costs (£)	Total LYGs	Total QALYs	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per QALY, £
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	54,397	0.916	0.702	77,502

Inc = Incremental; LYG = life-year gained; QALY = quality-adjusted life-year.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis (for 1,000 iterations) are presented in Table 55, which also presents results from the deterministic analysis for comparison. The probabilistic ICER versus pemetrexed + cisplatin or carboplatin was £77,127 per QALY gained compared with £77,502 per QALY gained in the deterministic analysis.

Figure 41 presents the cost-effectiveness acceptability curve. This shows that nivolumab + ipilimumab has a 0%, 0%, and 1% probability of being cost-effective at willingness-to-pay thresholds of £20,000, £30,000, and £50,000 per QALY.

Figure 42 presents the cost-effectiveness plane, which shows that most of the 1,000 iterations were in the northeast quadrant. This means that nivolumab + ipilimumab resulted in more QALYs and higher costs compared with pemetrexed + cisplatin or carboplatin.

Table 55. Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Deterministic results					
Nivolumab + ipilimumab	[redacted]	[redacted]			
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	54,397	0.702	77,502
Probabilistic results					
Nivolumab + ipilimumab	[redacted]	[redacted]			
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	55,423	0.706	77,127

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Figure 41. Cost-effectiveness acceptability curve: nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin

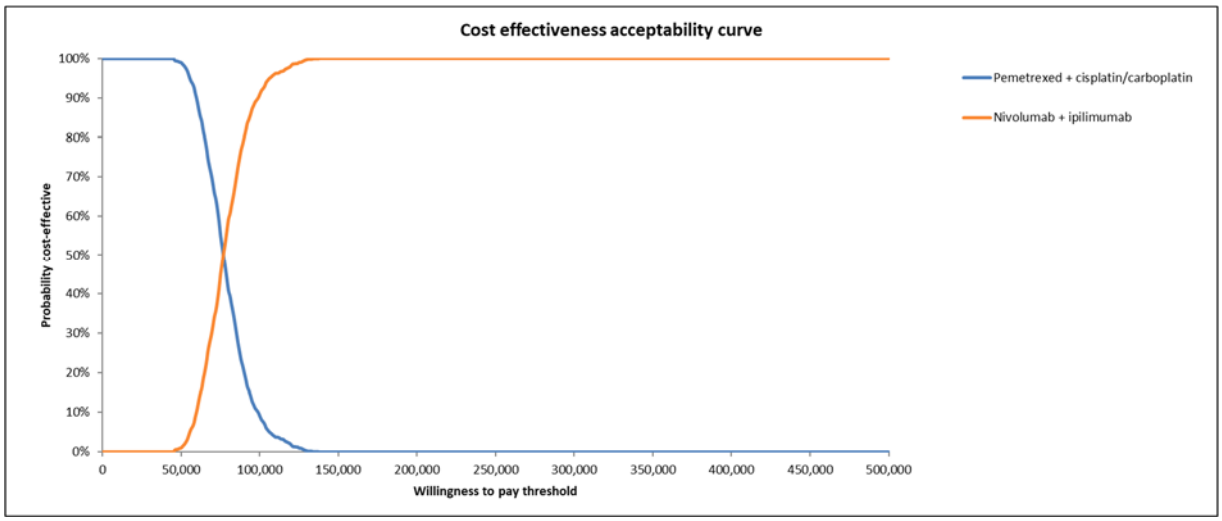
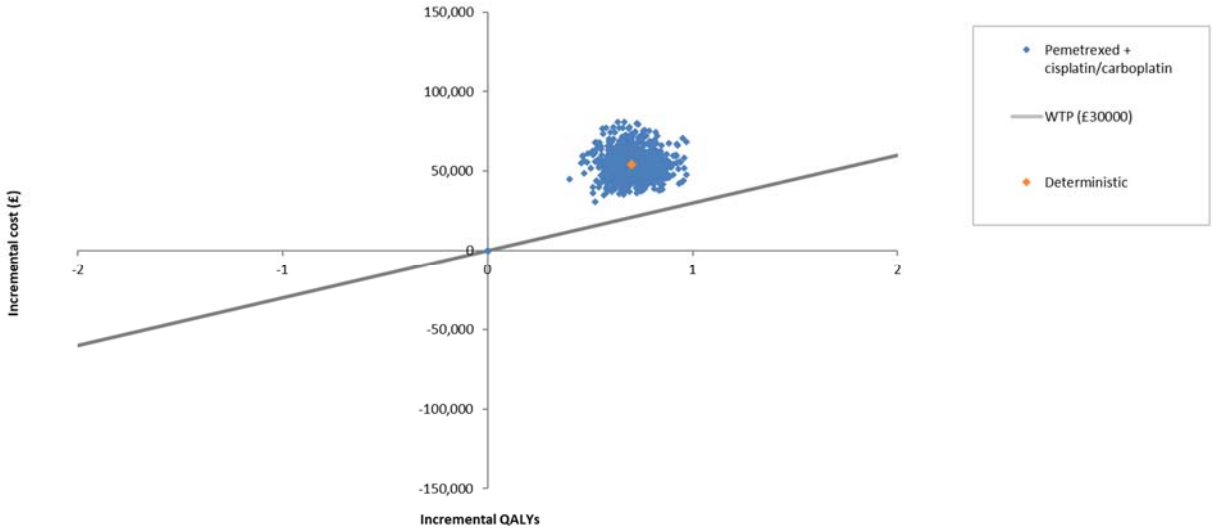


Figure 42. Cost-effectiveness plane: nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin



QALY = quality-adjusted life-year; WTP = willingness to pay threshold.

B.3.8.2 Deterministic sensitivity analysis

Table 56 summarises the deterministic sensitivity analyses for nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin. Figure 43 indicates that varying the treatment-specific health-state utility values by ± 20% had the largest impact on the ICER across the parameters tested.

Table 56. Deterministic sensitivity analysis results

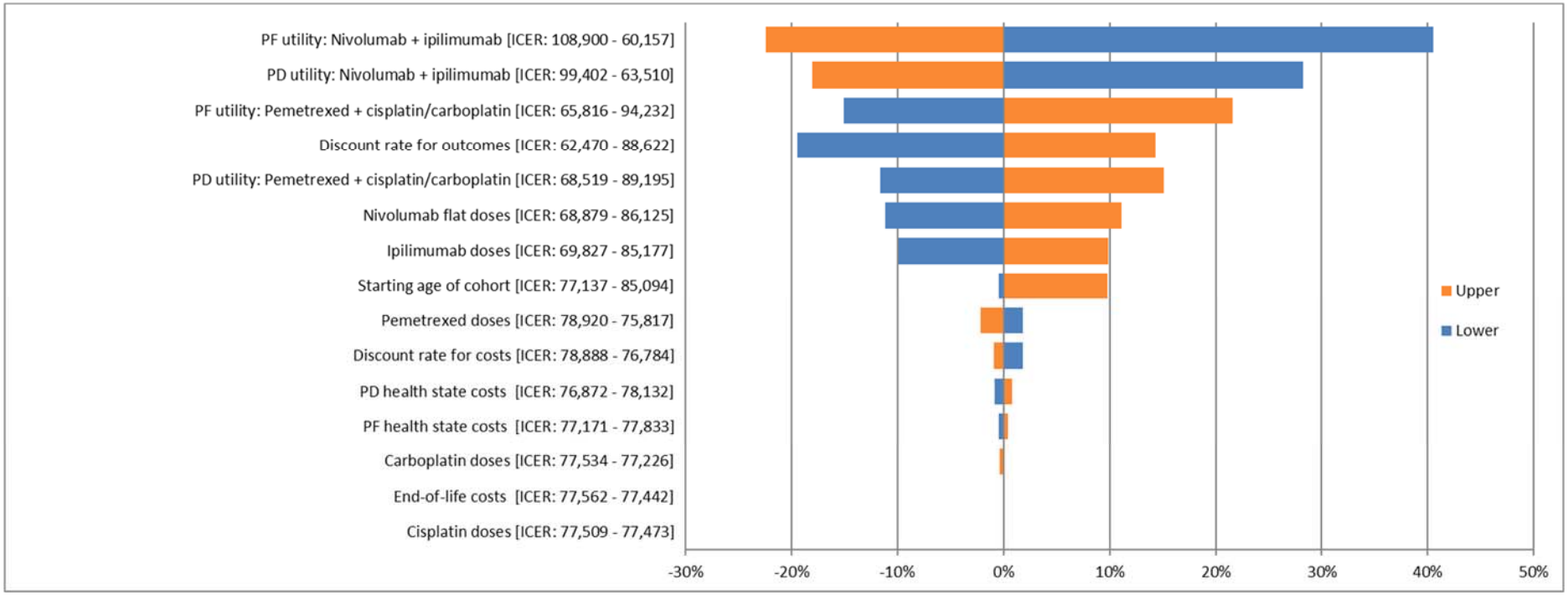
Parameter	Base-case value	Analysis	Values for DSA	Incremental cost per QALY (£)
Discount rate				
Cost discount rate	3.5%	Lower	0.0%	78,888
		Higher	6.0%	76,784
Outcome discount rate	3.5%	Lower	0.0%	62,470
		Higher	6.0%	88,622
Population				
Starting age of cohort	68.2 years	Lower	54.6 years	77,137
		Higher	81.8 years	85,094
Costs				
PF health-state costs	42.60	Lower	34.08	77,171
		Higher	51.12	77,833
PD health-state costs	107.85	Lower	86.28	76,872
		Higher	129.42	78,132
End of life costs	5,018.27	Lower	4,014.61	77,562
		Higher	6,021.92	77,442

Parameter	Base-case value	Analysis	Values for DSA	Incremental cost per QALY (£)
Mean number of doses				
Nivolumab	[redacted]	Lower	[redacted]	68,879
		Higher	[redacted]	86,125
Ipilimumab	[redacted]	Lower	[redacted]	69,827
		Higher	[redacted]	85,177
Pemetrexed	[redacted]	Lower	[redacted]	78,920
		Higher	[redacted]	75,817
Cisplatin	[redacted]	Lower	[redacted]	77,509
		Higher	[redacted]	77,473
Carboplatin	[redacted]	Lower	[redacted]	77,534
		Higher	[redacted]	77,226
Utilities				
PF: Nivolumab + ipilimumab	0.74	Lower	0.59	108,900
		Higher	0.88	60,157
PF: Pemetrexed + cisplatin or carboplatin	0.73	Lower	0.59	65,816
		Higher	0.88	94,232
PD: Nivolumab + ipilimumab	0.65	Lower	0.52	99,402
		Higher	0.78	63,510
PD: Pemetrexed + cisplatin or carboplatin	0.58	Lower	0.46	68,519
		Higher	0.70	89,195

DSA = deterministic sensitivity analysis; PD = progressed disease; PF = progression free; QALY = quality-adjusted life-year.

Note: Base-case values were varied ± 20%, except for discount rates.

Figure 43. Tornado diagram for deterministic sensitivity analysis of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin showing impact on the ICER



ICER = incremental cost-effectiveness ratio; PD = progressed disease; PF = progression free.

B.3.8.3 Scenario analysis

Scenario analyses were undertaken to investigate the effect of certain model inputs on costs and outcomes. The following scenarios were conducted:

- Scenario 1: independent hybrid log-normal OS curve for nivolumab + ipilimumab

  Scenario 2: independent log-logistic OS curve for nivolumab + ipilimumab and independent generalised gamma OS curve for PDC
- Scenario 3: independent log-logistic OS curves for nivolumab + ipilimumab and for PDC
- Scenario 4: second best fitting PFS curves based on AIC rank (log-normal for nivolumab + ipilimumab, generalised gamma for PDC)
- Scenario 5: treatment-independent utility values
- Scenario 6: use nivolumab weight-based dose
- Scenario 7: for the patients on pemetrexed therapy, 50% receive pemetrexed in combination with cisplatin and 50% receive pemetrexed in combination with carboplatin

Table 57 summarises the results of the scenario analyses.

Table 57. Results of scenario analyses

Scenario	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per LYG, £	Incremental costs per QALY, £	Difference from the base case (£, QALY)
Base case	54,397	0.916	0.702	59,416	77,502	
Scenario 1	54,725	0.974	0.740	56,171	73,935	−3,566
Scenario 2	54,896	1,008	0.756	54,441	72,592	−4,909
Scenario 3	53,303	0.710	0.582	75,098	91,561	14,059
Scenario 4	55,340	0.916	0.681	60,446	81,236	3,734
Scenario 5	54,397	0.916	0.634	59,416	85,832	8,330
Scenario 6	53,086	0.916	0.702	57,984	75,634	−1,867
Scenario 7	54,413	0.916	0.702	59,434	77,525	23

Inc = incremental; LY = life-year; LYG = life-year gained; QALY = quality-adjusted life-year.

B.3.8.4 Summary of sensitivity analyses results

As shown in Section B.3.8, the results of the sensitivity analyses are generally robust, but results are sensitive to some key parameters, including the selection of distributions for extrapolation of OS and the most appropriate health-state utility weights.

B.3.9 Subgroup analysis

No subgroup analyses were performed.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

As discussed in Section B.3.3, model predictions using the base-case survival extrapolations were checked against relevant external data sources to ensure that they are clinically plausible.

B.3.10.1.1 External expert validation

During the development of the economic model, external clinical and health economic experts were consulted to ensure an appropriate approach was taken and that the model had clinical validity. This included the following (meeting notes are included in Appendix N):

- A UK clinical advisory board meeting was held on 10 September 2020. Eight UK consultant oncologists, one UK consultant oncology nurse, and one UK consultant thoracic pathologist were included in the discussions.
- HTA advisory meetings were held in November 2020. Two consultant medical oncologists from large NHS oncology centres in England were included in the discussions.
- A global economic advisory board was held in November 2020 and included UK health economists and UK clinicians.

B.3.11 Interpretation and conclusions of economic evidence

This is the first economic evaluation undertaken for nivolumab + ipilimumab in an untreated unresectable MPM population; therefore, there are no published economic analyses with which to compare.

B.3.11.1 Generalisability of the results to clinical practice in England and relevance to all patients as identified in the decision problem

The analysis is likely to be directly applicable to clinical practice in England as follows:

- The patient population in CheckMate-743 and the economic analysis reflect patients with untreated unresectable MPM treated in the UK. Therefore, the clinical outcomes (PFS and OS) are likely to be applicable to the patient population in England.
- The economic model structure is in line with other oncology models[87,100,106,125] and previous MPM submissions to NICE.[2]
- The resource use and costs in the analysis have been validated by UK clinicians (Appendix N) and were sourced from UK-based publications (e.g., NHS Reference Costs[118] and the British National Formulary[114]) and previous NICE technology appraisals.[2,87,100,106,107,125]

The economic evaluation is relevant to all adults with unresectable MPM who would currently be considered for treatment with PDC (pemetrexed + cisplatin or carboplatin).

B.3.11.2 Strengths and weaknesses of the evaluation

The economic model is underpinned by patient-level data from CheckMate-743, which included efficacy, treatment duration, treatment patterns, and HRQOL of both nivolumab + ipilimumab and PDC. Because of shorter follow-up in the clinical trial than the model time horizon, survival extrapolation was essential to quantify the survival benefit beyond the study period. A robust and comprehensive approach was followed to ensure the survival extrapolation methods were statistically sound but also clinically plausible and reflective of real-world clinical practice. In terms of resource utilisation, all inputs were validated and aligned with previous NICE technology appraisals and identified from UK sources.

B.3.11.3 Further analyses that could be conducted

The cost-effectiveness analysis is based on immature OS data from CheckMate-743. Therefore, longer-term OS data will be important to confirm the survival extrapolations included in the current economic analysis. BMS recognise this uncertainty in the extrapolation of long-term OS data and therefore have proposed that this appraisal is a candidate for the CDF to allow for more data to be collected.

B.3.11.4 Concluding the economic analyses

In CheckMate-743, nivolumab + ipilimumab showed improved OS versus PDC in patients with unresectable MPM.

In the cost-effectiveness model, the improved survival for patients treated with nivolumab + ipilimumab resulted in an increase of 0.702 QALYs versus PDC when modelled over 20 years. This resulted in an ICER of £77,502 per QALY. Nivolumab + ipilimumab offers an innovative, clinically effective treatment option in the untreated unresectable MPM setting that is plausibly cost-effective.

As presented in Section B.3.3, the current OS extrapolations result in conservative assumptions of long-term treatment effect of nivolumab + ipilimumab compared with PDC. This is because decreased long-term hazards and thus a survival plateau are anticipated in the long-term based on the mechanisms of action of nivolumab and ipilimumab and clinical expert input. The current data cut of CheckMate-743 does not yet provide mature enough data for this plateau to have developed. Thus, longer-term data is anticipated to lead to reduced ICERs. This situation was seen in the NICE appraisals of nivolumab for previously treated squamous and non-squamous NSCLC,[86,87] in which the initial company base-case extrapolations, which were deemed overly optimistic by the ERG, were, in fact, found to be pessimistic when longer follow-up and real-world evidence, collected via the SACT database during the CDF period, were available for the CDF exit review. Similar results will be seen as the CheckMate-743 data become more mature. We anticipate that if nivolumab + ipilimumab is approved via the CDF, longer follow-up and real-world analyses based on data collected through the SACT database will be able to confirm this.

B.4 References

1. Woolhouse I, Bishop L, Darlison L, De Fonseka D, Edey A, Edwards J, et al. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. Thorax. 2018 Mar;73(Suppl 1):i1-i30.
2. NICE. Technology appraisal guidance [TA135]: pemetrexed for the treatment of malignant pleural mesothelioma. National Institute for Health and Care Excellence; 23 January 2008. Available at: https://www.nice.org.uk/guidance/ta135. Accessed 25 September 2020.
3. NHS England. NHS standard contract for cancer: malignant mesothelioma (adult). National Health Service England; 2013. Available at: https://www.england.nhs.uk/wp-content/uploads/2013/06/b10-cancer-mal-mesot.pdf. Accessed 10 August 2020.
4. Bristol-Myers Squibb. Nivolumab + ipilimumab: final clinical study report for study CA209743. 3 August 2020.
5. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011 Dec;480(7378):480-9.
6. Guo L, Zhang H, Chen B. Nivolumab as programmed death-1 (PD-1) inhibitor for targeted immunotherapy in tumor. J Cancer. 2017;8(3):410-6.
7. Wang C, Thudium KB, Han M, Wang XT, Huang H, Feingersh D, et al. In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. Cancer Immunol Res. 2014 Sep;2(9):846-56.
8. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010 Jul 1;28(19):3167-75.
9. Weber J. Ipilimumab: controversies in its development, utility and autoimmune adverse events. Cancer Immunol Immunother. 2009 May;58(5):823-30.
10. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci USA. 2007 Feb 27;104(9):3360-5.
11. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012 Mar 22;12(4):252-64.
12. Das R, Verma R, Sznol M, Boddupalli CS, Gettinger SN, Kluger H, et al. Combination therapy with anti-CTLA-4 and anti-PD-1 leads to distinct immunologic changes in vivo. J Immunol. 2015 Feb 1;194(3):950-9.
13. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov. 2018 Sep;8(9):1069-86.
14. Wei SC, Sharma R, Anang NAS, Levine JH, Zhao Y, Mancuso JJ, et al. Negative co-stimulation constrains T cell differentiation by imposing boundaries on possible cell states. Immunity. 2019 Apr 16;50(4):1084-98 e10.
15. Chae YK, Arya A, Iams W, Cruz MR, Chandra S, Choi J, et al. Current landscape and future of dual anti-CTLA4 and PD-1/PD-L1 blockade immunotherapy in cancer; lessons learned from clinical trials with melanoma and non-small cell lung cancer (NSCLC). J Immunother Cancer. 2018 May 16;6(1):39.
16. Bristol-Myers Squibb. Press release: European Medicines Agency validates Bristol-Myers Squibb's type II variation application for Opdivo (nivolumab) plus Yervoy (ipilimumab) for first-line treatment of malignant pleural mesothelioma. 15 September 2020. Available at: https://news.bms.com/news/details/2020/European-Medicines-Agency-Validates-Bristol-Myers-Squibbs-Type-II-Variation-Application-for-Opdivo-nivolumab-Plus-Yervoy-ipilimumab-for-First-line-Treatment-of-Malignant-Pleural-Mesothelioma/default.aspx. Accessed 11 November 2020.
17. OPDIVO Draft SmPC. OPDIVO (nivolumab) draft summary of product characteristics, version 1.0. August 2020.

18. Baas P. First-line nivolumab + ipilimumab vs chemotherapy in unresectable malignant pleural mesothelioma: CheckMate 743 [oral presentation]. Presented at the World Conference on Lung Cancer Virtual Presidential Symposium; 8 August 2020.
19. Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet. 2021 Jan 21.
20. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015 Jul 2;373(1):23-34.
21. Goldman JW, Antonia S, Gettinger S, Borghaei H, Brahmer J, Ready N, et al. Nivolumab plus ipilimumab as first-line treatment for advanced NSCLC: 2-year overall survival and long-term outcomes from CheckMate 012. Presented at the American Society of Clinical Oncology; 2-6 June 2017. Chicago, IL, USA.
22. Jia W, Gao Q, Han A, Zhu H, Yu J. The potential mechanism, recognition and clinical significance of tumor pseudoprogression after immunotherapy. Cancer Biol Med. 2019 Nov;16(4):655-70.
23. Frelaut M, du Rusquec P, de Moura A, Le Tourneau C, Borcoman E. Pseudoprogression and hyperprogression as new forms of response to immunotherapy. BioDrugs. 2020 Aug;34(4):463-76.
24. Scherpereel A, Opitz I, Berghmans T, Psallidas I, Glatzer M, Rigau D, et al. ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma. Eur Respir J. 2020;55(6):1900953.
25. NCCN. NCCN clinical practice guidelines in oncology (NCCN Guidelines®) for malignant pleural mesothelioma. Version 1.2020. National Comprehensive Cancer Network; 27 November 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf. Accessed 31 July 2020.
26. ACS. What is malignant mesothelioma? American Cancer Society; 2018. Available at: https://www.cancer.org/cancer/malignant-mesothelioma/about/malignant-mesothelioma.html. Accessed 31 July 2020.
27. Mesothelioma.com. Types of mesothelioma. 2020. Available at: https://www.mesothelioma.com/mesothelioma/types/. Accessed 10 August 2020.
28. Cancer Research UK. Mesothelioma statistics. 2020. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/mesothelioma#heading-Zero. Accessed 31 July 2020.
29. Bibby AC, Tsim S, Kanellakis N, Ball H, Talbot DC, Blyth KG, et al. Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment. Eur Respir Rev. 2016 Dec;25(142):472-86.
30. Mesothelioma UK. About mesothelioma. 2020. Available at: https://www.mesothelioma.uk.com/information/about-mesothelioma/. Accessed 31 July 2020.
31. Bianco A, Valente T, De Rimini ML, Sica G, Fiorelli A. Clinical diagnosis of malignant pleural mesothelioma. J Thorac Dis. 2018;10(Suppl 2):S253-61.
32. Royal College of Physicians. National mesothelioma audit report 2020 (for the audit period 2016-18). May 2020. Available at: https://www.rcplondon.ac.uk/projects/outputs/national-mesothelioma-audit-report-2020-audit-period-2016-18. Accessed 10 August 2020.
33. American Joint Committee on Cancer. Pleural mesothelioma. AJCC cancer staging manual. 7th ed. New York, NY: Springer; 2010.
34. Inai K. Pathology of mesothelioma. Environ Health Prev Med. 2008 Mar;13(2):60-4.
35. Mansfield AS, Roden AC, Peikert T, Sheinin YM, Harrington SM, Krco CJ, et al. B7-H1 expression in malignant pleural mesothelioma is associated with sarcomatoid histology and poor prognosis. J Thorac Oncol. 2014 Jul;9(7):1036-40.

36. Hotta K, Fujimoto N. Current evidence and future perspectives of immune-checkpoint inhibitors in unresectable malignant pleural mesothelioma. J Immunother Cancer. 2020;8(1):e000461.
37. Brosseau S, Danel C, Scherpereel A, Mazières J, Lantuejoul S, Margery J, et al. Shorter survival in malignant pleural mesothelioma patients with high PD-L1 expression associated with sarcomatoid or biphasic histology subtype: a series of 214 cases from the Bio-MAPS cohort. Clin Lung Cancer. 2019 Sep;20(5):e564-e75.
38. Cedrés S, Ponce-Aix S, Zugazagoitia J, Sansano I, Enguita A, Navarro-Mendivil A, et al. Analysis of expression of programmed cell death 1 ligand 1 (PD-L1) in malignant pleural mesothelioma (MPM). PLoS One. 2015;10(3):e0121071.
39. Thapa B, Salcedo A, Lin X, Walkiewicz M, Murone C, Ameratunga M, et al. The immune microenvironment, genome-wide copy number aberrations, and survival in mesothelioma. J Thorac Oncol. 2017 May;12(5):850-9.
40. Nguyen BH, Montgomery R, Fadia M, Wang J, Ali S. PD-L1 expression associated with worse survival outcome in malignant pleural mesothelioma. Asia Pac J Clin Oncol. 2018 Feb;14(1):69-73.
41. Sobhani N, Roviello G, Pivetta T, Ianza A, Bonazza D, Zanconati F, et al. Tumour infiltrating lymphocytes and PD-L1 expression as potential predictors of outcome in patients with malignant pleural mesothelioma. Mol Biol Rep. 2019 Jun;46(3):2713-20.
42. Scherpereel A, Mazieres J, Greillier L, Lantuejoul S, Dô P, Bylicki O, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. Lancet Oncol. 2019 Feb;20(2):239-53.
43. Popat S, Curioni-Fontecedro A, Dafni U, Shah R, O'Brien M, Pope A, et al. A multicentre randomised phase III trial comparing pembrolizumab versus single-agent chemotherapy for advanced pre-treated malignant pleural mesothelioma: the European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial. Ann Oncol. 2020 Dec;31(12):1734-45.
44. Baas P, Daumont MJ, Lacoin L, Penrod J, Carroll R, Tanna N. Treatment patterns and outcomes in malignant pleural mesothelioma in England: a nationwide CAS registry analysis from the I-O Optimise initiative [poster 1909P]. Presented at the European Society for Medical Oncology Virtual Congress; 19-21 September 2020.
45. Health and Safety Executive. Mesothelioma statistics for Great Britain, 2020. 2020. Available at: https://www.hse.gov.uk/statistics/causdis/mesothelioma/mesothelioma.pdf. Accessed 12 November 2020.
46. G. B. D. Occupational Carcinogens Collaborators. Global and regional burden of cancer in 2016 arising from occupational exposure to selected carcinogens: a systematic analysis for the Global Burden of Disease Study 2016. Occup Environ Med. 2020 Mar;77(3):151-9.
47. Amin W, Linkov F, Landsittel D, Silverstein J, Bashara W, Gaudioso C, et al. Factors influencing malignant mesothelioma survival: a retrospective review of the National Mesothelioma Virtual Bank cohort [version 3; peer review: 2 approved, 1 approved with reservations]. F1000Research. 2019;7(1184).
48. Bates GE, Hashmi AK, Bressler T, Zajac J, Hesdorffer M, Taub RN. Approach to offering remote support to mesothelioma patients: the mesothelioma survivor project. Transl Lung Cancer Res. 2016 Jun;5(3):216-8.
49. Mercadante S, Degiovanni D, Casuccio A. Symptom burden in mesothelioma patients admitted to home palliative care. Curr Med Res Opin. 2016 Dec;32(12):1985-8.
50. Arnold DT, Hooper CE, Morley A, White P, Lyburn ID, Searle J, et al. The effect of chemotherapy on health-related quality of life in mesothelioma: results from the SWAMP trial. Br J Cancer. 2015 Mar;112(7):1183-9.
51. Bottomley A, Gaafar R, Manegold C, Burgers S, Coens C, Legrand C, et al. Short-term treatment-related symptoms and quality of life: results from an international

randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an EORTC Lung-Cancer Group and National Cancer Institute, Canada, Intergroup Study. J Clin Oncol. 2006 Mar;24(9):1435-42.
52. Granieri A, Tamburello S, Tamburello A, Casale S, Cont C, Guglielmucci F, et al. Quality of life and personality traits in patients with malignant pleural mesothelioma and their first-degree caregivers. Neuropsychiatr Dis Treat. 2013;9:1193-202.
53. Arber A, Spencer L. 'It's all bad news': the first 3 months following a diagnosis of malignant pleural mesothelioma. Psychooncology. 2013 Jul;22(7):1528-33.
54. Dietrich K, Zhan LJ, Herman M, Nagaratnam S, Corbett K. Routine Edmonton Symptom Assessment System (ESAS) scores in epithelioid malignant pleural mesothelioma (eMPM) patients undergoing palliative systemic therapy. J Clin Oncol. 2019;37(31 Suppl):96.
55. Clayson H. Suffering in mesothelioma: concepts and contexts. Prog Palliat Care. 2003;11(5):251-5.
56. Boyer M, Jassem J, Liepa A, Symanowski J, Kaukel E, Denham A, et al. Symptom and quality of life advantages for pemetrexed + cisplatin vs cisplatin in treatment of malignant pleural mesothelioma [O 56] [abstract]. Presented at the International Association for the Study of Lung Cancer World Conference on Lung Cancer; 10-14 August 2003. Vancouver, Canada.
57. Muers MF, Stephens RJ, Fisher P, Darlison L, Higgs CM, Lowry E, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. Lancet. 2008 May 17;371(9625):1685-94.
58. van Meerbeeck JP, Gaafar R, Manegold C, Van Klaveren RJ, Van Marck EA, Vincent M, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. J Clin Oncol. 2005 Oct 1;23(28):6881-9.
59. Daumont M, Nwokeji E, Lubeck D, Gleeson M, Penrod JR, Danese M. Treatment patterns and outcomes in advanced malignant pleural mesothelioma: surveillance, Epidemiology, and end results (SEER) Medicare Linked Data [poster P1.06-13]. Presented at the International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer; 7-10 September 2019. Barcelona, Spain.
60. Watterson A, Gorman T, Malcolm C, Robinson M, Beck M. The economic costs of health service treatments for asbestos-related mesothelioma deaths. Ann N Y Acad Sci. 2006 Sep;1076:871-81.
61. van Zandwijk N, Clarke C, Henderson D, Musk AW, Fong K, Nowak A, et al. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. J Thorac Dis. 2013;5(6):E254-307.
62. Alimta SmPC. Alimta (pemetrexed disodium) summary of product characteristics. Eli Lilly; 29 May 2020. Available at: https://www.medicines.org.uk/emc/product/3862/smpc. Accessed 10 August 2020.
63. Baas P, Fennell D, Kerr KM, Van Schil PE, Haas RL, Peters S. Malignant pleural mesothelioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v31-9.
64. NICE/NHS England. NG161 NHS England interim treatment options during the COVID-19 pandemic. National Institute for Health and Care Excellence/National Health Service England; 22 October 2020. Available at: https://www.nice.org.uk/guidance/ng161/resources/nhs-england-interim-treatment-options-during-the-covid19-pandemic-pdf-8715724381. Accessed 26 October 2020.
65. Clinicaltrials.gov. NCT02139904: Vinorelbine in Mesothelioma (VIM). 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT02139904. Accessed 19 August 2020.

66. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003 Jul;21(14):2636-44.
67. Ceresoli GL, Aerts JG, Dziadziuszko R, Ramlau R, Cedres S, van Meerbeeck JP, et al. Tumour treating fields in combination with pemetrexed and cisplatin or carboplatin as first-line treatment for unresectable malignant pleural mesothelioma (STELLAR): a multicentre, single-arm phase 2 trial. Lancet Oncol. 2019 Dec;20(12):1702-9.
68. Castagneto B, Botta M, Aitini E, Spigno F, Degiovanni D, Alabiso O, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). Ann Oncol. 2008 Feb;19(2):370-3.
69. Ceresoli GL, Zucali PA, Favaretto AG, Grossi F, Bidoli P, Del Conte G, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. J Clin Oncol. 2006 Mar;24(9):1443-8.
70. Santoro A, O'Brien ME, Stahel RA, Nackaerts K, Baas P, Karthaus M, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaïve patients with malignant pleural mesothelioma: results of the International Expanded Access Program. J Thorac Oncol. 2008 Jul;3(7):756-63.
71. Cisplatin SmPC. Cisplatin summary of product characteristics. Hospira UK, Ltd.; 2020. Available at: https://www.medicines.org.uk/emc/product/3788/smpc. Accessed 10 August 2020.
72. Carboplatin SmPC. Carboplatin summary of product characteristics. Hospira UK, Ltd.; 2020. Available at: https://www.medicines.org.uk/emc/product/3787/smpc. Accessed 10 August 2020.
73. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet. 2016 Apr 2;387(10026):1405-14.
74. ClinicalTrials.gov. Study of nivolumab combined with ipilimumab versus pemetrexed and cisplatin or carboplatin as first line therapy in unresectable pleural mesothelioma patients (CheckMate743). NCT02899299. 2020. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02899299. Accessed 31 July 2020.
75. Bristol-Myers Squibb data on file. Clinical protocol CA209743: a phase III, randomized, open label trial of nivolumab in combination with ipilimumab versus pemetrexed with cisplatin or carboplatin as first line therapy in unresectable pleural mesothelioma. 25 April 2019.
76. FDA. Clinical trial endpoints for the approval of cancer drugs and biologics: guidance for industry. Food and Drug Administration; December 2018. Available at: https://www.fda.gov/media/71195/download. Accessed 11 August 2018.
77. Scagliotti G, Gaafar R, Nowak A, Nakano T, Van Meerbeeck J, Popat S, et al. Nintedanib + pemetrexed/cisplatin in patients with unresectable MPM: phase III results from the LUME-Meso trial. Presented at the International Association for the Study of Lung Cancer (IASLC) 19th World Conference on Lung Cancer; 23-26 September 2018. Toronto, Canada.
78. Bristol-Myers Squibb. Analyses of quality of life endpoints in CA209743 (CheckMate 743), a phase 3, randomized, open-label trial of nivolumab in combination with ipilimumab versus pemetrexed with cisplatin or carboplatin as first line therapy in unresectable pleural mesothelioma. 17 November 2020.
79. Hollen PJ, Gralla RJ, Kris MG, Cox C, Belani CP, Grunberg SM, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Psychometric assessment of the Lung Cancer Symptom Scale. Cancer. 1994 Apr 15;73(8):2087-98.
80. Sarna L, Swann S, Langer C, Werner-Wasik M, Nicolaou N, Komaki R, et al. Clinically meaningful differences in patient-reported outcomes with amifostine in combination

with chemoradiation for locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. Int J Radiat Oncol Biol Phys. 2008 Dec 1;72(5):1378-84.
81. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007 Dec 21;5:70.
82. NICE. Single technology appraisal: PMG24: user guide for company evidence submission template. National Institute for Health and Care Excellence; 2015. Available at: https://www.nice.org.uk/process/pmg24/chapter/clinical-effectiveness. Accessed 14 September 2020.
83. Albiges L, Tannir NM, Burotto M, McDermott D, Plimack ER, Barthelemy P, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open. 2020 Nov;5(6).
84. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2019 Oct 17;381(16):1535-46.
85. Bristol-Myers Squibb. Press release: U.S. Food and Drug Administration Approves Opdivo® (nivolumab) + Yervoy® (ipilimumab) as the first and only immunotherapy treatment for previously untreated unresectable malignant pleural mesothelioma. 2 October 2020. Available at: https://investors.bms.com/iframes/press-releases/press-release-details/2020/U.S.-Food-and-Drug-Administration-Approves-Opdivo-nivolumab--Yervoy-ipilimumab-as-the-First-and-Only-Immunotherapy-Treatment-for-Previously-Untreated-Unresectable-Malignant-Pleural-Mesothelioma/default.aspx. Accessed 12 November 2020.
86. NICE. Technology appraisal guidance [TA655]: nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy National Institute for Health and Care Excellence; 21 October 2020. Available at: https://www.nice.org.uk/guidance/ta655. Accessed 26 November 2020.
87. NICE. Nivolumab for previously treated non-squamous non-small-cell lung cancer [TA484]. National Institute for Health and Care Excellence; 2017. Available at: https://www.nice.org.uk/guidance/ta484. Accessed 9 July 2018.
88. Cordony A, Le Reun C, Smala A, Symanowski JT, Watkins J. Cost-effectiveness of pemetrexed plus cisplatin: malignant pleural mesothelioma treatment in UK clinical practice. Value Health. 2008 Jan-Feb;11(1):4-12.
89. Woods B, Paracha D, Scott A, Thatcher N. Raltitrexed plus cisplatin is cost-effective compared with pemetrexed plus cisplatin in patients with malignant pleural mesothelioma. Lung Cancer. 2012;75(2):261-7.
90. Rintoul RC, Ritchie AJ, Edwards JG, Waller DA, Coonar AS, Bennett M, et al. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. Lancet. 2014 Sep 20;384(9948):1118-27.
91. Stewart S, Clive A, Maskell NA, Penz E. Evaluating quality of life and cost implications of prophylactic radiotherapy in mesothelioma: health economic analysis of the SMART trial. PLoS One. 2018;13(2).
92. Zhan M, Zheng H, Xu T, Yang Y, Li Q. Cost-effectiveness analysis of additional bevacizumab to pemetrexed plus cisplatin for malignant pleural mesothelioma based on the MAPS trial. Lung Cancer. 2017 Aug;110:1-6.
93. Malacan J, Carlson JJ. Cost-effectiveness analysis of addition of bevacizumab to a standard chemotherapy doublet (pemetrexed + cisplatin) in patients with malignant pleural mesothelioma. Value Health. 2016;19(3).
94. Kogut S, Babcock Z. Estimating the potential cost effectiveness of maintenance therapy following chemotherapy for malignant mesothelioma. Value Health. 2016;19(3).

95. Chetty M, Cordony A, Davey K, Karampela K, Le Reun C, Watt M. Pcn1 economic impact of adopting pemetrexed plus cisplatin for malignant pleural mesothelioma into scottish clinical practice. Value Health. 2005;8(6).
96. Davey P, Cordony A, Rajan N, Arora B, Pavlakis N. Value-for-money of pemetrexed plus cisplatin versus cisplatin alone in the treatment of malignant pleural mesothelioma. Value Health. 2005;8(3):238-9.
97. Woods B, Sideris E, Palmer S, Latimer N, M. S. NICE DSU technical support document 19. Partitioned survival analysis for decision modelling in health care: A critical review. 2017. Available at: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf. Accessed 9 November 2020.
98. NICE. Guide to the methods of technology appraisal 2013. National Institute for Health and Care Excellence; 4 April 2013. Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed 17 November 2020.
99. Antonia SJ, Borghaei H, Ramalingam SS, Horn L, De Castro Carpeno J, Pluzanski A, et al. Four-year survival with nivolumab in patients with previously treated advanced non-small-cell lung cancer: a pooled analysis. Lancet Oncol. 2019 Oct;20(10):1395-408.
100. NICE. Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer [TA531]. Committee papers. National Institute for Health and Care Excellence; 2018. Available at: https://www.nice.org.uk/guidance/ta531/documents/committee-papers. Accessed 23 July 2018.
101. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data 2013. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf. Accessed 26 November 2020.
102. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012 Feb 1;12:9.
103. Burnham K, Anderson D. Model selection and multimodel inference: a practical information-theoretic approach; 2004.
104. Raftery AE. Bayesian model selection in social research. Sociol Methodol. 1995;25:111-63.
105. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-e52.
106. NICE. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (TA584). National Institute for Health and Care Excellence; 2019. Available at: https://www.nice.org.uk/guidance/TA584. Accessed 1 September 2020.
107. NICE. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy. National Institute for Health and Care Excellence; 2017. Available at: https://www.nice.org.uk/guidance/ta428/resources/pembrolizumab-for-treating-pdl1positive-nonsmallcell-lung-cancer-after-chemotherapy-pdf-82604670410437. Accessed 2 August 2018.
108. NICE. Technology appraisal guidance [TA612]: Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab. 20 November 2019 2019. Available at: https://www.nice.org.uk/guidance/ta612. Accessed 26 November 2020.
109. Bagust A, Beale S. Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: an alternative approach. Med Decis Making. 2014 Apr;34(3):343-51.
110. Latimer NR. Response to “Survival analysis and extrapolation modeling of time-to-event clinical trial data for economic evaluation: An alternative approach” by Bagust and Beale. Medical Decision Making. 2014;34(3):279-82.

111. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008 Oct 21;6:84.
112. Lloyd A, van Hanswijck de Jonge P, Doyle S, Cornes P. Health state utility scores for cancer-related anemia through societal and patient valuations. Value Health. 2008 Dec;11(7):1178-85.
113. Attard CL, Brown S, Alloul K, Moore MJ. Cost-effectiveness of folfirinox for first-line treatment of metastatic pancreatic cancer. Curr Oncol. 2014 Feb;21(1):e41-51.
114. British National Formulary. 2020. Available at: https://bnf.nice.org.uk/. Accessed June 2020.
115. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). 4 March 2020. Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed 25 November 2020.
116. OPDIVO SmPC. OPDIVO (nivolumab) summary of product characteristics. Bristol-Myers Squibb; 2020. Available at: https://www.medicines.org.uk/emc/product/6888. Accessed 30 July 2020.
117. YERVOY SmPC. YERVOY (ipilimumab) summary of product characteristics. Bristol-Myers Squibb; 15 July 2020. Available at: https://www.medicines.org.uk/emc/product/4683. Accessed 30 July 2020.
118. NHS Improvement. NHS reference costs 2018/2019. 19 February 2020. Available at: https://improvement.nhs.uk/resources/national-cost-collection/. Accessed 3 June 2020.
119. Waterhouse D, Nwokeji E, Boyd M, Penrod JR, Espirito J, Robert NJ, et al. Treatment patterns and outcomes of advanced malignant pleural mesothelioma (MPM) patients in a community practice setting [poster]. Presented at the International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer; 7-10 September 2019. Barcelona, Spain.
120. Curtis L. Unit costs of health and social care 2019. UK, Kent: 2019. Available at: https://kar.kent.ac.uk/79286/. Accessed 24 November 2020.
121. NICE. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis [TA199]. National Institute for Health and Care Excellence; 25 August 2010. Available at: https://www.nice.org.uk/guidance/ta199. Accessed 16 November 2020.
122. Curtis L. Unit costs of health and social care 2015. Personal Social Services Research Unit; 2015. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2015/. Accessed 27 July 2018.
123. Brown T, Pilkington G, Bagust A, Boland A, Oyee J, Tudur-Smith C, et al. Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation. Health Technol Assess. 2013 Jul;17(31):1-278.
124. NICE. Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leaukaemia [ID671]. National Institute for Health and Care Excellence; 2017. Available at: https://www.nice.org.uk/guidance/ta451/documents/committee-papers-2. Accessed 27 July 2018.
125. NICE. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer: technology appraisal [TA192]. National Institute for Health and Care Excellence; 28 July 2010. Available at: http://www.nice.org.uk/guidance/ta192. Accessed 15 May 2015.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Clarification questions

18 February 2021

File name	Version	Contains confidential information	Date
ID1609 nivolumab_ERG clarification questions_ Responses FINAL_18Feb21_[redacted].docx	1.0	**Yes**	18 Feb 2021

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A1. The following are questions regarding the literature searches:

a) MEDLINE is reported as being searched via Embase.com. Please clarify the impact of including only Emtree indexing terms rather than MeSH in the search as not all the journals indexed in MEDLINE are indexed with EMTREE in Embase.

For publications that are also indexed by Elsevier/Embase (source journals common to both databases), the original Embase indexing is used. For publications that are unique to MEDLINE, the MEDLINE indexing is mapped to Emtree. Indexed MEDLINE records are delivered to Elsevier daily and are incorporated into Embase after deduplication with records already indexed by Elsevier to produce so-called MEDLINE-unique records.

MEDLINE-unique records are not re-indexed by Elsevier. However, their indexing is mapped to Emtree terms used in Embase. This is done to ensure that Emtree terminology can be used to search all Embase records, including those originally derived from MEDLINE.

When MeSH terms are mapped to Emtree, subheadings are mapped to Emtree subheadings. Since not all MeSH subheadings have an exact Emtree equivalent, some of them generate Emtree terms rather than subheadings. During search strategy development, we also mapped the entry terms in the MeSH description to identify search terms. Thereby, using a combination of Emtree and MeSH terminology along with free-text terms, terms for limits, wherever applicable, we have ensured maximum discoverability of biomedical evidence relevant to our PICOS.

b) Please confirm the host used to search the Cochrane Library as the syntax appears to be the same as the Wiley interface.

Wiley online interface was used to search the Cochrane Library.

c) Please provide details of study design filters employed in the searches for clinical effectiveness studies (Appendix D), cost-effectiveness studies (Appendix H), health-related quality of life studies (Appendix I) and also provide references for any filters used.

Research-based adapted filters for finding cost-effectiveness studies, health-related quality of life studies, randomised trials, and other study designs were based on the filters developed by Scottish Intercollegiate Guidelines Network (SIGN), InterTASC Information Specialists' Sub-Group (ISSG) website, National Health Service Economic Evaluation Database (NHS EED), Canadian Agency for Drugs and Technologies in Health (CADTH), and British Medical Journal (BMJ) Best Practice. Search strings were adapted from previously published filters used to identify clinical, cost-effectiveness and health-related quality of life studies. Please see the online links below with search keywords also populated in Table 1, Table 2, and Table 3.

SIGN (for clinical and economic reviews):
https://www.sign.ac.uk/what-we-do/methodology/search-filters/

ISSG (for clinical, economic, and quality of life reviews):
https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home

NHS EED (for economic review):
https://www.crd.york.ac.uk/crdweb/searchstrategies.asp

BMJ Best Practice (for clinical review):
https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/

CADTH (for economic, quality of life, and clinical reviews):
https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#health

Table 1. Cost-effectiveness studies

'Cost' NEAR/2 (effective* OR efficien* OR utilit* OR minimi* OR consequen* OR benefit* OR unit* OR estimate* OR variable*)
'budget impact analysis' OR 'budget impact model' OR ('budget impact' NEAR/3 (method* OR analys* OR model* OR simulation* OR assessment*)) OR 'BIA'
'economic evaluation'/syn OR 'economic model'/syn OR 'pharmacoeconomics'/syn
'markov' NEAR/3 (method* OR analys* OR model* OR simulation* OR assessment* OR chain*) OR 'hidden markov model'/syn OR 'Markov chain'/syn
'monte carlo method'/syn OR ('monte carlo' NEAR/3 (method* OR analys* OR model* OR simulation* OR assessment* OR chain*)) OR 'Monte Carlo simulation' OR 'Monte Carlo technique'
'cost effectiveness analysis'/syn OR (('cost effectiveness' OR 'cost effective') NEAR/3 (method* OR analys* OR model* OR simulation* OR assessment*)) OR 'cost effectiveness ratio' OR 'cost effectiveness' OR 'cost-effectiveness' OR 'CEA' OR 'CER'
'cost efficiency analysis'/exp OR ('cost efficiency' NEAR/3 (method* OR analys* OR model* OR simulation* OR assessment*)) OR 'cost efficiency' OR 'cost-efficiency'
'cost benefit analysis'/syn OR ('cost benefit' NEAR/3 (method* OR analys* OR model* OR simulation* OR assessment*)) OR 'cost benefit' OR 'cost-benefit' OR 'cost benefit ratio' OR 'cost-benefit ratio' OR 'CBA' OR 'CBR'
'cost utility analysis'/syn OR (('cost utility' OR 'cost utilities') NEAR/3 (method* OR analys* OR model* OR simulation* OR assessment*)) OR 'cost utility' OR 'cost-utility' OR 'CUA'
'cost minimization analysis'/syn OR (('cost minimization' OR 'cost minimisation') NEAR/3 (method* OR analys* OR model* OR simulation* OR assessment*)) OR 'cost minimisation' OR 'cost minimization' OR 'cost-minimisation' OR 'cost-minimization' OR 'CMA'
'cost consequence analysis'/exp OR ('cost consequence' NEAR/3 (method* OR analys* OR model* OR simulation* OR assessment*)) OR 'cost consequence' OR 'cost- consequence' OR 'CCA'
(('cost' OR 'economic') NEAR/3 (method* OR analys* OR model* OR simulation* OR assessment*)) OR ('Health economic' NEXT/1 stud*) OR 'decision analytic' OR 'decision-analytic'
'economics'/de OR 'economic aspect' OR 'cost'/de OR 'health care cost' OR 'drug cost' OR 'hospital cost' OR 'socioeconomics' OR 'health economics' OR 'fee' OR 'budget' OR 'hospital finance' OR 'financial management' OR 'health care financing' OR 'low cost' OR 'high cost' OR (health*care NEXT/1 cost*) OR ('health care' NEXT/1 cost*) OR 'fiscal' OR 'funding' OR 'financial' OR 'finance' OR ('unit' NEXT/1 cost*) OR price* OR 'pricing'
(Econ* NEAR/2 ('Burden' OR 'disease' OR 'assessment')) OR (Cost* NEAR/2 (illness* OR health* OR 'burden' OR 'disease' OR 'assessment'))
('Out' NEAR/2 'Pocket') OR (Patient* NEAR/2 Cost*) OR copay* OR (Privat* NEAR/2 Expendit*) OR ((Carer* OR Caregiv*) NEAR/2 (Cost* OR Expendit* OR 'Time'))
('Value' NEAR/2 ('Money' OR 'Monetary')) OR (cost* NEAR/3 (treat* OR therap*))
'Costly' OR 'Costing' OR pharmacoeconomic* OR pharmaco-economic* OR 'Finances' OR 'Financed' OR 'cost analysis' OR 'cost assessment' OR 'cost study'
'societal cost' OR 'social cost' OR 'social care cost' OR 'out of pocket' OR 'patient cost' OR 'co-payment' OR 'private expenditure' OR 'patient time' OR 'carer cost' OR 'carer expenditure' OR 'carer time' OR 'caregiver cost' OR 'caregiver expenditure' OR 'caregiver time' OR 'economic burden' OR 'cost burden' OR 'resource burden' OR 'financial burden' OR 'economic consequences' OR 'cost of illness' OR 'healthcare cost' OR 'cost of disease'

Table 2. Clinical effectiveness studies

'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR 'rct' OR 'random

allocation' OR 'randomly allocated' OR 'allocated randomly' OR placebo* OR 'prospective study'/de OR (‘allocated’ NEAR/2 ‘random’) OR (random* NEAR/1 assign*) OR random* OR (‘single’ OR ‘double’ OR ‘triple’ OR ‘treble’) NEAR/1 (blind* OR mask*) NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de)
'nrct' OR ‘n rct’ OR n?rct OR (('non' OR 'not') NEAR/3 ('randomised' OR 'randomized')) OR ‘controlled clinical trial’ OR ‘controlled trial’
'cohort study' OR cohort*:ab,ti OR (('follow up' OR ‘followup’) NEXT/1 (‘study’ OR ‘studies’)):ab,ti OR 'retrospective study'/syn OR 'cohort analysis'/exp OR 'longitudinal study'/syn OR 'prospective study'/syn OR 'longitudinal' OR 'retrospective' OR 'prospective' OR 'observational study'/syn OR (‘cohort’ NEXT/1 stud*) OR (‘cohort’ NEXT/1 analy*) OR 'register'/de OR (‘database’ NEAR/2 ‘study’) OR (‘real’ NEAR/2 ‘world’) OR ('healthcare' NEXT/1 ‘record’)
‘questionnaire’ OR survey* OR 'real-world' OR 'observational' OR 'routine clinical practice' OR 'clinical practice' OR 'clinical practice setting' OR ((‘medical’ OR ‘insurance’) AND (‘claims’ OR ‘claim’ OR 'claims database' OR 'claim database')) OR 'other observational study' OR 'naturalistic trial' OR 'practical clinical trial' OR 'pragmatic trial' OR 'real-world clinical trial' OR 'pragmatic clinical trial' OR 'chart review' OR ‘survey’ OR 'medical record review' OR ‘naturalistic study’ OR ‘naturalistic’
(‘observational’ NEXT/1 stud*) OR 'cross sectional’ OR ‘cross-sectional’ OR ‘cross-sectional study’/syn

Table 3. Health-related quality of life studies

‘quality of life’/syn OR ‘health related quality of life’/exp OR ‘health-related quality of life’/exp
‘HRQoL’/exp OR ‘HRQL’/exp OR ‘QoL’/exp OR ‘Quality life’ OR ‘Life quality’
‘quality adjusted life’ OR ‘quality-adjust-life’ OR ‘qaly’ OR ‘qald’ OR ‘qale’ OR ‘qtime’ OR ‘Quality-adjusted life year’ OR ‘Quality-adjusted life days’ OR ‘Quality-adjusted life expectancy’ OR ‘Quality adjusted life year’ OR ‘Quality adjusted life days’ OR ‘Quality adjusted life expectancy’
‘WHO QOL-BREF’ OR ‘QOL-BREF’ OR ‘World Health Organization Quality of Life scale’
‘WHO-QOL’ OR ‘WHO QOL’ OR ‘WHOQOL’
‘EORTC QLQ C-30’ OR ‘EORTC QLQ C30’ OR ‘EORTC QLQ C 30’ OR ‘EORTC QLQ-C30’ OR ‘EORTC core quality of life questionnaire’
‘Rotterdam symptom checklist’ OR ‘Rotterdam’ OR ‘RSCL’
'visual analog scale' OR ('visual' NEXT/1 analog* AND analog* NEXT/1 scale*) OR 'VAS'
‘LCSS Meso’ OR ‘Lung cancer symptom scale’ OR ‘LCSS’
‘EORTC QLQ LC-13’ OR ‘EORTC QLQ LC13’ OR ‘EORTC QLQ LC 13’ OR ‘EORTC QLQ-LC13’
‘Lung cancer-specific quality of life questionnaire’
‘sf6D’ OR ‘sf 6D’ OR ‘sf-6D’ OR ‘short form 6D’ OR ‘shortform 6D’ OR ‘shortform6D’
‘sf6’ OR ‘sf 6’ OR ‘sf-6’ OR ‘short form 6’ OR ‘shortform 6’ OR ‘shortform6’ OR ‘sf six’ OR ‘shortform six’ OR ‘short form six’ OR ‘Short-Form 6-Dimensions’ OR ‘Short-Form 6’
‘sf12’ OR ‘sf 12’ OR ‘sf-12’ OR ‘short form 12’ OR ‘shortform 12’ OR ‘shortform12’ OR ‘sf twelve’ OR ‘shortform twelve’ OR ‘short form twelve’
‘sf36’ OR ‘sf 36’ OR ‘sf-36’ OR ‘short form 36’ OR ‘shortform 36’ OR ‘shortform36’ OR ‘sf thirtysix’ OR ‘sf thirty six’ OR ‘shortform thirtysix’ OR ‘shortform thirty six’ OR ‘short form thirtysix’ OR ‘short form thirty six’
‘sf20’ OR ‘sf 20’ OR ‘sf-20’ OR ‘short form 20’ OR ‘shortform 20’ OR ‘shortform20’ OR ‘sf twenty’ OR ‘shortform twenty’ OR ‘short form twenty’
'euroqol' OR 'euro-qol' OR 'euro qol' OR 'eq5d' OR 'eq-5d' OR 'eq 5d'
'utility':ab,ti OR utilit*:ab,ti OR ('health' NEAR/2 utilit*):ab,ti OR 'health state utility':ab,ti OR 'hsuv' OR 'health state utility value':ab,ti
('health' AND (‘state’ NEXT/1 utilit*)) OR ‘utility score’ OR ‘health utility’ OR disutility*
(‘health’ NEXT/1 state* AND state* NEXT/1 preference*)
health*year*equivalent:ab,ti OR ‘hye’:ab,ti OR ‘hyes’:ab,ti
'health utility index':ab,ti OR 'hui':ab,ti OR ‘hui1’:ab,ti OR ‘hui2’:ab,ti OR ‘hui3’:ab,ti
(utilit* NEAR/2 (measure* OR outcome* OR state* OR ‘health’ OR score* OR weight* OR ‘analysis’ OR ‘analyses’)):ab,ti
‘Rosser’ OR ‘willingness to pay’ OR (‘willingness’ NEAR/2 ‘pay’) OR ('discrete choice' NEXT/1 experiment*)

(utilit* NEXT/1 (score* OR value* OR evaluation*))
‘standard gamble’ OR (‘standard’ NEAR/2 gamble*)
‘Time trade off’ OR ‘time tradeoff’ OR ‘time trade-off’ OR (‘time’ NEAR/2 trade*off) OR ‘TTO’
'visual analog scale' OR ('visual' NEXT/1 analog* AND analog* NEXT/1 scale*) OR 'VAS'
‘Health status indicator’:ab,ti OR ‘activities of daily living’:ab,ti OR ‘Health survey’:ab,ti
‘disability adjusted life’ OR ‘daly’

d) Please provide a breakdown of hits for the CDSR and CENTRAL searches in Appendix D (page 9 and 15), and for the different Cochrane Library databases searched for cost-effectiveness (page 57 of Appendix H) and health-related quality of life studies (Appendix I).

Table 4 presents the breakdown of search hits for the different Cochrane Library databases searched for clinical effectiveness, health-related quality of life, and cost-effectiveness reviews.

Table 4. Number of hits identified in the different Cochrane databases, by review

Review type	CENTRAL	CDSR	CCA	NHS EED	DARE	HTAD
Clinical effectiveness	366	35	1	(-)	(-)	(-)
Health-related quality of life*	188	43	(-)	(-)	(-)	(-)
Cost-effectiveness**	10	0	(-)	5	22	8

*Combined hits reported for separate searches conducted for QoL and utility reviews
**Search hits reported only from economic evaluations review (in alignment with PRISMA). However, studies identified from cost & resource use review (with separate search strategy) were also cross-checked to identify any additional publications

e) Please provide URLs, search terms used and the number of results for each of the conference proceedings searches reported in Appendix D (page 24).

Table 5 presents details related to search terms used, URLs, and search hits for all conference proceedings searches. We screened abstracts from the annual/biennial meetings (2018, 2019, 2020) with disease indication terms in the abstract database by relevant research categories.

Table 5. Summary of conference proceedings searches

Conference name	Year	URL	Search keywords	Hits
ASCO	2020	https://meetinglibrary.asco.org/results/(Keywords:"Mesothelioma");page=0?	Mesothelioma OR Malignant pleural mesothelioma OR MPM OR Pleural mesothelioma	44
ASCO	2019			44
ASCO	2018			59
ESMO	2020	https://www.sciencedirect.com/search?qs=mesothelioma&pub=Ann		39
ESMO	2019			34

Conference name	Year	URL	Search keywords	Hits
ESMO	2018	als%20of%20Oncology&cid=321639&years=2020&lastSelectedFacet=years	Mesothelioma OR Malignant pleural mesothelioma OR MPM OR Pleural mesothelioma	14
ISPOR Europe	2020	Not searched*		
ISPOR Europe	2019	https://www.ispor.org/heor-resources/presentations-database/search	Mesothelioma OR Malignant pleural mesothelioma OR MPM OR Pleural mesothelioma	0
ISPOR Europe	2018			0
ISPOR Asia Pacific	2020	https://www.ispor.org/heor-resources/presentations-database/search	Mesothelioma OR Malignant pleural mesothelioma OR MPM OR Pleural mesothelioma	0
ISPOR Asia Pacific	2018			0
ISPOR Latin America	2019	https://www.ispor.org/heor-resources/presentations-database/search	Mesothelioma OR Malignant pleural mesothelioma OR MPM OR Pleural mesothelioma	0
ISPOR US	2020	https://www.ispor.org/heor-resources/presentations-database/search	Mesothelioma OR Malignant pleural mesothelioma OR MPM OR Pleural mesothelioma	1
ISPOR US	2019			0
ISPOR US	2018			0
WCLC	2020	Not searched*		
WCLC	2019	https://wclc2019.iaslc.org/wp-content/uploads/2019/08/WCLC2019-Abstract-Book_web-friendly.pdf	Mesothelioma, Malignant pleural mesothelioma, MPM, Pleural mesothelioma	PDF (-)
WCLC	2018	https://wclc2018.iaslc.org/wp-content/uploads/2018/09/WCLC2018-Abstract-Book_vF-LR-REV-SEPT-25-2018.pdf	Mesothelioma, Malignant pleural mesothelioma, MPM, Pleural mesothelioma	PDF (-)
ELCC	2020	Not searched*		
ELCC	2019	https://www.sciencedirect.com/journal/annals-of-oncology/vol/30/suppl/S2?page=3#article-201	Mesothelioma	4
ELCC	2018	https://www.jto.org/issue/S1556-0864(18)X0004-5	Mesothelioma OR Malignant pleural mesothelioma OR MPM OR Pleural mesothelioma	98
IMIG	2020	Not searched*		
IMIG	2018	Not available		
AACR	2020	https://www.aacr.org/meeting/aacr-annual-meeting-2020/abstracts/ https://cancerres.aacrjournals.org/content/80/16_Supplement	Mesothelioma, Malignant pleural mesothelioma, MPM, Pleural mesothelioma	(-)
AACR	2019	https://www.aacr.org/professionals/meetings/previous-aacr-meetings/previous-aacr-meetings-2019/ https://cancerres.aacrjournals.org/content/79/13_Supplement	Mesothelioma, Malignant pleural mesothelioma, MPM, Pleural mesothelioma	(-)
AACR	2018	https://www.aacr.org/professionals/meetings/previous-aacr-meetings/previous-aacr-meetings-2018/	Mesothelioma, Malignant pleural mesothelioma, MPM, Pleural mesothelioma	(-)

*Conducted outside the review timeframe, i.e., after October 2020 due to cancellation or postponement of the conference; (-): Search hits not countable; the conference was searched by screening through multiple research categories

f) Please provide a rationale for including study design filters in the original Cochrane Library search strategy for cost-effectiveness studies and health-related quality of life studies.

The search strategy for economic evaluations consisted of two main concepts of interest: 1) disease, 2) economics. There was no restriction on the interventions. A systematic search should use relevant PICO items combined with an economic search filter in the general bibliographic databases such as Embase and PubMed. We agree that there is no formal requirement to add an economic evaluation search filter to searches within economic evaluation databases, e.g., NHS EED, because they are pre-filtered. But we are more cautious using this approach because of the peculiarities of different databases, including Cochrane. It has been observed that Cochrane sometimes does not select studies on the basis that they meet the criteria for being classified as full economic evaluations. Instead, studies are selected based on the inclusion criteria set for the effectiveness review (focusing on randomised trials). As such, this set of Cochrane reviews considers only those economics studies conducted alongside studies eligible for inclusion in the effectiveness review. This may exclude relevant data in full economic evaluations based on data from sources other than RCTs, other economics studies, or partial economic evaluations (e.g., costing studies). The CENTRAL database has also been observed to include some cost publications. Thereby, we use the searches tailored explicitly to the retrieval of relevant economics studies (all-inclusive) with a general aim to maximise sensitivity and precision. We used a similar approach for the identification of HRQoL studies. Also, restricting the HRQoL search to “disease” and “CENTRAL” limits only would have resulted in low sensitivity and precision as the results would have also comprised clinical effectiveness studies with no quality of life components evaluated.

Decision problem

A2. Priority question. The decision problem specified in the scope defines the population as adults with untreated, unresectable MPM. The inclusion criteria reported for CheckMate-743 (Table 7 of the CS) specifies patients with ECOG PS 0-1. The company have also not provided a comparison with BSC, as argued in Table

1, because '…first-line systematic anticancer therapies are only used in patients with good PS (0-1), in accordance with BTS guidelines.'

g) Please confirm that the evidence presented is for patients with untreated unresectable MPM and ECOG PS 0-1 only.

All the clinical evidence in Section B.2 of the submission to support nivolumab + ipilimumab is from CheckMate-743, which included patients with unresectable MPM and ECOG PS0-1 only. For the economic evidence in B.3, clinical outcomes and utilities used in the economic model are also from CM-743 so only includes patients with unresectable MPM and ECOG PS0-1.

In real-life clinical practice in England, a high proportion of patients with MPM have unknown PS. The 2016-2018 UK National Mesothelioma Audit showed approximately half (51.4%) of patients with MPM had ECOG PS 0-1, but 19.4% of patients had missing status data.[1] This is supported by real-world data from the CAS registry in England from January 2013-December 2017 that showed of 3,159 unresected patients who received first-line pemetrexed + platinum-based therapy, 55% were PS0-1, 8.4% were PS≥2 and 36.7% were unknown PS.[2]

h) Please confirm if the proposed marketing authorisation wording includes any restriction by ECOG PS.

The proposed marketing authorisation does not include any restriction by ECOG PS. It is standard clinical practice for systemic anticancer treatment to be used only in patients with MPM with good PS (ECOG 0-1), as recommended by the British Thoracic Society guideline.[3]

i) If it is not the case that the evidence presented is for patients with untreated unresectable MPM and ECOG PS 0-1 only, but is for the wider population without any ECOG PS restriction then please include a comparison with BSC.

Not applicable as per response to A.1(g) – the rationale for this decision is also supported by the two clinical experts who validated the submission (Appendix N) and also by the British Thoracic Oncology Group in their consultation comments on the draft scope, who stated "*BSC is not an appropriate comparator because this*

technology relates to a particular group of fit patients for whom this would not be deemed acceptable unless specifically requested by the patient".

j) How many patients were excluded from the CheckMate-743 trial based on ECOG PS.

Of 713 patients enrolled in the trial, 108 patients were excluded, resulting in 605 randomised patients. Of the 108 excluded patients, 84 patients no longer met the inclusion criteria, which would include some patients who were no longer classed as PS0-1 (inclusion criterion 2e). Appendix 2.4 of the CSR states that 13 patients were excluded due to worsening PS or no longer met study criterion 2e.

A3. Priority question. In support of the omission of raltitrexed as a comparator, the CS states that: 'The BTS guidelines state that pemetrexed can be replaced with raltitrexed and cisplatin can be replaced with carboplatin as alternatives; however, in clinical practice, raltitrexed is not used in the UK NHS.' The main reference given for treatment patterns is the 2016-2018 UK National Mesothelioma Audit; this report does not describe the chemotherapy regimens received by patients who did not receive pemetrexed with carboplatin or cisplatin (32%) and does not mention raltitrexed. The company do provide expert opinion in Appendix N that raltitrexed is not used, but this is only from two clinicians. Please either provide further evidence that raltitrexed is not currently used in the UK NHS or include raltitrexed as a comparator.

The rationale for excluding raltitrexed was supported by the two UK clinical experts who validated the submission (Appendix N) and also by the British Thoracic Oncology Group in their consultation comments on the draft scope, who stated *"raltitrexed is essentially not used in the 1st line setting within the UK. This is because there isn't a definable subgroup of patients who would not be appropriate for cisplatin pemetrexed but would be appropriate for cisplatin raltitrexed. It is also unlicensed."*

In addition, detailed real-world treatment data from the CAS registry in England from January 2013-December 2017 show there was no recorded use of raltitrexed during the study period. In total, 3,159 unresected patients received first-line SACT; of these, 90.2% received PDC (platinum-based therapy + pemetrexed), and 4.8%

received their first-line therapy in a clinical trial; the proportion receiving PDC as a first-line therapy was similar across histopathologies.[2,4]

Lack of use of raltitrexed is also supported by 2019 data from a real-world cross-sectional study on treatment patterns in Europe, which included 248 patients from the UK (Table 6). In the UK in 2019, [redacted].[5]

Table 6. EU5 cross-sectional study: UK treatment patterns

		UK				
		Overall	Epithelioid	Biphasic	Sarcomatoid	Unknown
Total number of patients		[redacted]				
Group 1 - Doublet chemotherapy	**Total - Group 1 - Doublet chemotherapy (n, %)**	[redacted]				
	Pemetrexed + Platinum	[redacted]				
	Carboplatin, Pemetrexed	[redacted]				
	Carboplatin, Pemetrexed disodium	[redacted]				
	Cisplatin, Pemetrexed	[redacted]				
	Cisplatin, Pemetrexed disodium	[redacted]				
	Raltitrexed + Platinum	[redacted]				
	Carboplatin, Raltitrexed	[redacted]				
	Cisplatin, Raltitrexed	[redacted]				
Group 2 - Triplet chemotherapy	**Total - Group 2 - triplet chemotherapy (n, %)**	[redacted]				
	Pemetrexed + platinum + bevacizumab	[redacted]				
	Bevacizumab, Cisplatin, Pemetrexed	[redacted]				
		[redacted]				

Group 3 - Single agent chemotherapy	**Total - Group 3 - single agent chemotherapy (n, %)**	[redacted]				
	Pemetrexed	[redacted]				
	Pemetrexed	[redacted]				
	Other chemotherapy	[redacted]				
	Vinorelbine	[redacted]				
	Platinum	[redacted]				
	Carboplatin	[redacted]				
	Raltitrexed	[redacted]				
	Raltitrexed	[redacted]				
Group 4 - Others	**Total - Group 4 - others (n, %)**	[redacted]				
	Immunotherapy (IO)	[redacted]				
	Immunotherapy e.g., PD-1/L1	[redacted]				
	Other chemotherapy + platinum	[redacted]				
	Carboplatin, Gemcitabine	[redacted]				

Source: Moore[5]

A4. Priority question. The company have chosen the combination of pemetrexed plus either cisplatin or carboplatin as comparator i.e. not to separate into two comparators on the basis that which was received in CheckMate-743 was according to investigator choice. Also, the CSR states: “The use of cisplatin was preferred; however, carboplatin may be used at the discretion of the investigator.“ However, the BTS guideline recommends carboplatin only: “Where cisplatin is contraindicated, or has adverse risk,” (p.i2). Therefore, there appears to be a clinically identifiable subgroup who would be prescribed carboplatin instead of cisplatin.

a) Please provide evidence that the choice of either cisplatin or carboplatin in the trial is according to the same clinical criteria as in England NHS practice or, if this is not the case, please discuss the likely implications of any discrepancy.

The choice of cisplatin or carboplatin in CheckMate-743 was according to investigator choice, in line with clinical practice in the UK, where both cisplatin and carboplatin is used. In CM-743, 74% of the PDC arm were treated with carboplatin (209 of 284) and 37% were treated with cisplatin (104 of 284), which is similar to reported real-world treatment patterns in the NHS in England, as described below.

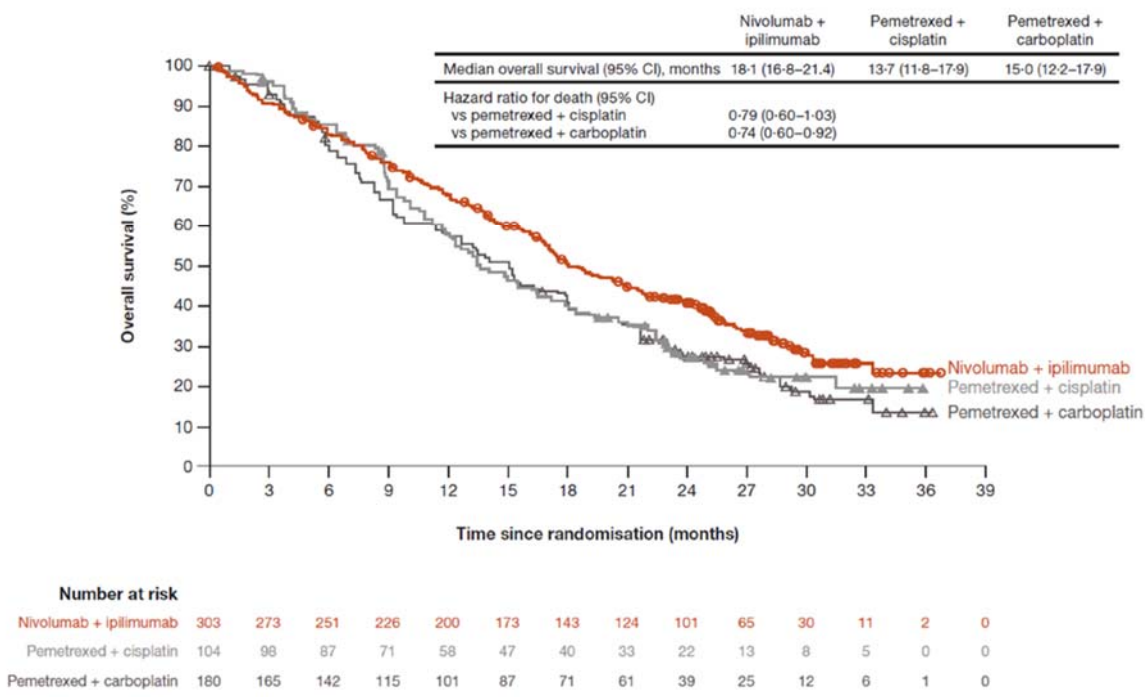
The UK National Mesothelioma Audit 2020 reported that in those patients who received chemotherapy, pemetrexed with carboplatin was the most common regimen used (48%), followed by pemetrexed with cisplatin (20%).[1] In addition, real-world treatment data from the CAS registry in England from January 2013-December 2017 reported use of both carboplatin and cisplatin during the study period.[4] Of patients treated with PDC, [redacted].[4] This is also supported by data from the EU cross-sectional study including a smaller cohort of 248 UK patients (Table 6). In the UK, [redacted].[5]

The rationale for investigator choice of cisplatin/carboplatin was supported by the two UK clinical experts who validated the submission (Appendix N; one of whom used carboplatin exclusively and the other who used both carboplatin and cisplatin) and also by the British Thoracic Oncology Group in their consultation comments on the draft scope, who stated that *"the "real life" NHS standard will be carboplatin and pemetrexed despite what NICE and other guidelines state. Only a proportion receive cisplatin. For logistical and chemo unit chair time reasons, carboplatin is often given instead of cisplatin based on an assumption that the two are equally efficacious."*

b) Could the company either treat pemetrexed plus cisplatin and pemetrexed plus carboplatin as separate comparators and thus provide complete separate clinical effectiveness results or justify why this is either not required or inappropriate.

Overall survival was similar between chemotherapy regimens: median overall survival was 13.7 months (95% CI 11.8–17.9) with pemetrexed plus cisplatin, and 15.0 months (12.2–17.9) with pemetrexed plus carboplatin.[6]

Figure 1. Overall survival by PDC regimen received at cycle 1



Notes: Minimum and median follow-up for overall survival were 22.1 and 29.7 months, respectively. Of patients randomised to the chemotherapy group, 18 (6.0%) never received treatment.

Source: Baas et al.[6]

Clinical effectiveness equivalence of these two PDC regimens was widely accepted by the UK clinical experts, based on key published data from an expanded access programme of 1,704 chemotherapy-naive subjects with MPM, where the confirmed response rates, time-to-progression and 1-year survival using pemetrexed + carboplatin and pemetrexed + cisplatin were similar.[7]

A5. Priority question. Nivolumab dosing in the trial was according to weight, but the cost-effectiveness analysis employed a flat nivolumab dosage of 360 mg every 3 weeks, which was stated to align with the anticipated EMA licence. Please provide evidence that this difference in dosing will have no effect on effectiveness, quality of life or safety.

The dosing and schedule of nivolumab in CheckMate-743 (3 mg/kg every 2 weeks, Q2W) differs from the proposed indicated dose and schedule of nivolumab submitted to the European Medicines Agency (EMA) (360 mg every 3 weeks, Q3W). Nivolumab dosed using a 3mg/kg Q2W schedule with ipilimumab 1 mg/kg every 6 weeks (Q6W) for first-line MPM was approved by the FDA on 2 October 2020[8] and

is the standard nivolumab dose used in a range of lung cancer indications recommended by NICE, including for the second-line treatment of squamous and non-squamous NSCLC.[9,10]

Based on the totality of pharmacokinetic modelling of nivolumab exposure, exposure-efficacy, exposure-safety, and clinical subgroup efficacy and safety analyses, the balance of benefits and risks of nivolumab 360 mg Q3W is expected to be similar to that of nivolumab 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W for the treatment of untreated unresectable MPM. The flat dosing of nivolumab was explored in a pharmacometric and clinical subgroup analysis by body weight, which was presented at the ESMO Immuno-Oncology Virtual Congress December 9–12 2020.[11] This study assessed any potential associations between body weight with efficacy or safety of nivolumab + ipilimumab, with focus on higher body weight for efficacy and lower body weight for safety. Model-predicted mean probabilities for OS and grade 2+ IMAEs were comparable between nivolumab 360 mg Q3W, 240 mg Q2W, and 3 mg/kg Q2W, in combination with ipilimumab 1 mg/kg Q6W. Clinical subgroup analysis from CheckMate-743 showed that survival was not compromised in patients with higher body weight while no additional safety concerns were observed in patients with lower body weight. Overall, these results suggest that the benefit-risk of flat-dose nivolumab + ipilimumab regimens are comparable with nivolumab 3 mg/kg Q2W + ipilimumab, supporting alternative dosing regimens in patients with previously untreated, unresectable MPM.

CheckMate-743 trial

A6. The CS (Table 7) includes the information that 6/103 study sites for the CheckMate-743 trial are in the UK. Please confirm that the total number of UK study participants was 38/605.

Yes - CM-743 included 38 participants at 6 UK study sites.

A7. Priority question. The CS (section 2.6.1) states that the results presented are from the interim analysis, based on a database lock 3rd April 2020.

a) Can the company please indicate whether and when any further data cuts and the analyses of results will be available, before the estimated study completion date for CheckMate-743 in April 2022.

As CheckMate-743 met its primary endpoint at the 3 April 2020 database lock, this analysis was considered the final analysis. However, follow up of CM-743 is ongoing and additional data cuts are expected, likely in xxxxxxxxx (TBC). As the timing of the analysis is event driven, there is uncertainty on the exact timing of future database locks.

b) Please provide analyses on the most recently available data and incorporate these into the cost-effectiveness analysis.

The company submission includes the most recent data cut available at this time, which is the database lock of 3rd April 2020.

A8. The clinical effectiveness results, for CheckMate-743, presented in the CS (Table 13) do not include any formal statistical analyses of the comparison for all response outcomes (complete response, partial response, stable disease and progressive disease). Please confirm if no formal statistical analyses have been undertaken for these outcomes, or provide all results for any such analyses.

In CheckMate-743, no formal statistical testing of the secondary objectives was pre-specified and results were descriptive. Results were presented in the CS with their exact 2-sided 95% CIs by Clopper and Pearson (Table 13, page 41). Additional analyses of the response outcomes with 95% CIs are presented in **Error! Reference source not found.** below.

Table 7. Response rate per BICR

Outcome	Nivolumab + ipilimumab (n = 303)	PDC (n = 302)
ORR per BICR[a]		
ORR,[b] n (% [95% CI])	120/303 (39.6 [34.1-45.4])	129/302 (42.7 [37.1-48.5])
Median TTR, months	2.7	2.5
DOR (95% CI), months[c]	11.0 (8.1-16.5)	6.7 (5.3-7.1)
Best overall response, n (% [95% CI])		
CR,	5/303 (1.7 [0.5-3.8])	0 (0)
PR	115/303 (38.0 [32.5-43.7)	129/302 (42.7 [37.1-48.5)
Stable disease	112/303 (37.0 [31.5-42.7])	125/302 (41.4 [35.8-47.2])
Progressive disease	55/303 (18.2 [14.0-23.0])	14/302 (4.6 [2.6-7.7])
DCR (95% CI), % (CR+PR+SD)	76.6 (71.4-81.2)	85.1 (80.6-88.9)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; HR = hazard ratio; ORR = objective response rate; OS = overall survival; PDC = platinum-based doublet chemotherapy; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; TTR = time to response.

[a] Per adapted modified RECIST for pleural mesothelioma lesions and/or RECIST v1.1 for non-pleural lesions.

[b] 95% CI Clopper and Pearson Method.

[c] Kaplan-Meier estimates.

Source: Bristol-Myers Squibb[12]

A9. The CS (Table 14) also provides overall survival rates, for each treatment arm of CheckMate-743, at 6, 12, 18 and 24 months. Please also provide the results of formal statistical analyses for the comparison of these outcomes.

Formal statistical analysis of OS was compared in two randomised arms via a two-sided, log-rank test stratified by histology and gender at the interim analysis cut-off only. At the prespecified interim analysis (database lock: April 3, 2020), the median follow-up for overall survival was 29.7 months (IQR, 26·7–32·9), with a minimum of 22.1 months. Formal statistical analysis at the 2-sided 95% level was performed at the other time points, as presented in the CS (Document B, page 43).

A10. Please provide the results of formal statistical analyses for the comparison of all outcomes presented for the subgroup analysis according to PD-L1 expression (Table 15 in the CS).

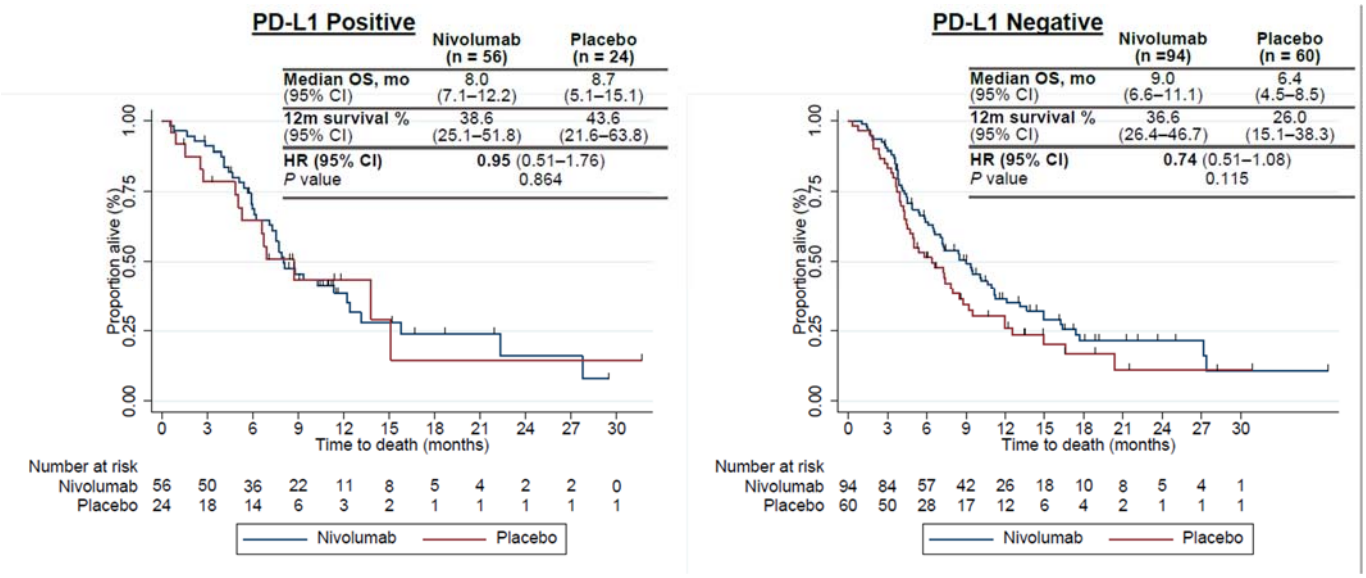
See response to A8; all available results with the PD-L1 subgroup have been presented in the company submission, including formal statistical analysis at the 2-sided 95% level. Please note that PD-L1 was not a stratification factor in CheckMate-743; therefore, these subgroup data are limited by potential imbalances in known or unknown prognostic factors because the role of PD-L1 in MPM is unclear. A

secondary objective of CheckMate-743 was to evaluate whether PD-L1 expression was a predictive biomarker for response outcomes for nivolumab + ipilimumab, as this is not established. Owing to the small sample size and event counts in the PD-L1–negative subgroup, the statistical analyses in the PD-L1 subgroups are descriptive in nature and should be interpreted with caution.

Evidence for the levels of PD-L1 expression in patients with MPM in England is inconsistent, with wide variation in the threshold cutoffs used and the rates of PD-L1 expression observed in clinical studies (see Table 3 in Document B, p17). As a result, large differences have been reported, with 20% to 70% of specimens tested being considered PD-L1-positive.[13] Unlike other lung cancers in which PD-L1 inhibitors are already approved and PD-L1 testing is standard practice, PD-L1 testing is not routinely performed on biopsies from patients with MPM in the NHS in England, and the thresholds, scoring methods, and antibodies used to detect PD-L1 expression in MPM are not standardised which may contribute to this variation. Reliable PD-L1 testing is highly dependent on biopsy, which is technically difficult in MPM because MPM tumours have spatial heterogeneity and the amount of tissue obtained is usually not sufficient for accurate PD-L1 testing. For these reasons and because until now no PD-L1 inhibitor has shown benefit in MPM in the first-line setting, PD-L1 testing is not currently a standard test in the NHS for this patient population (see clinical expert opinion: Appendix N).

CheckMate-743 is the first phase 3 RCT in first-line MPM with prospective results by PD-L1 expression. In CheckMate-743, the treatment effect of nivolumab + ipilimumab versus PDC was greater in the PD-L1 ≥1% than in the PD-L1 <1% subgroup. However, the greater treatment effect of immunotherapy with the PD-L1 ≥1% subtype was not observed in CONFIRM, a recent RCT that compared nivolumab monotherapy with placebo for the second-line treatment for MPM. Contrary to CheckMate-743, results from CONFIRM showed no difference in treatment effect with PD-L1 subtype (Figure 2).[14]

Figure 2. CONFIRM: overall survival by PD-L1* Tumour Proportion Score



*PD-L1 tumour proportion score (TPS). Immunochemistry was assessed using Dako22C3 PD-L1 antibody: negative < 1% TPS, positive ≥1%TPS

Source: Fennell[14]

For these reasons, the company considers the outcomes in the PD-L1 subgroups as descriptive in nature and should be interpreted with caution. In addition, due to the severe limitations in PD-L1 testing in MPM and the increased survival benefit seen in both PD-L1 <1% and ≥1% subgroups in CheckMate-743, the company does not consider patient selection criteria for nivolumab + ipilimumab by levels of PD-L1 expression as appropriate, given the high clinical unmet need and short life expectancy of all patients with unresectable MPM eligible for SACT.

A11. Section B.2.6.1.5 of the CS describes the results of subgroup analyses by histological subtype. This section only includes results for survival outcomes (OS and PFS). Please provide results of subgroup analyses by histological subtype for response outcomes, consistent with those provided for the full study population and for the PD-L1 expression subgroup analyses**.**

Histological subtype (epithelioid or non-epithelioid) was a stratification factor in CheckMate-743 and results for OS and PFS were presented in the company submission along with accompanying 95% CIs as appropriate. Assessment of ORR by BICR in all randomised patients and histology subtypes available in the CSR, along statistical analysis at the 2-sided 95% level is shown in **Error! Reference source not found.**.

Table 8. Objective Response Rate per BICR by Histology Subtype

	ORR[a] (%) (95% CI)	
	Nivolumab + ipilimumab (n = 303)	PDC (n = 302)
Overall	120/303 (39.6%) (34.1, 45.4)	129/302 (42.7%) (37.1, 48.5)
Epithelioid	88/229 (38.4%) (32.1, 45.1)	108/227 (47.6%) (40.9, 54.3)
Mixed	8/26 (30.8%) (14.3, 51.8)	11/28 (39.3%) (21.5, 59.4
Sarcomatoid	19/35 (54.3%) (36.6, 71.2)	9/36 (25.0%) (12.1, 42.2)
Other	5/13 (38.5%) (13.9, 68.4)	1/11 (9.1%) (0.2, 41.3)

CI = confidence interval; PDC = platinum-based doublet chemotherapy.
[a]CR+PR as per adapted m-RECIST for pleural mesothelioma and RECIST 1.1 criteria confirmation of response required (BICR Assessment), confidence interval based on the Clopper and Pearson method.
Source: Bristol-Myers Squibb[12]

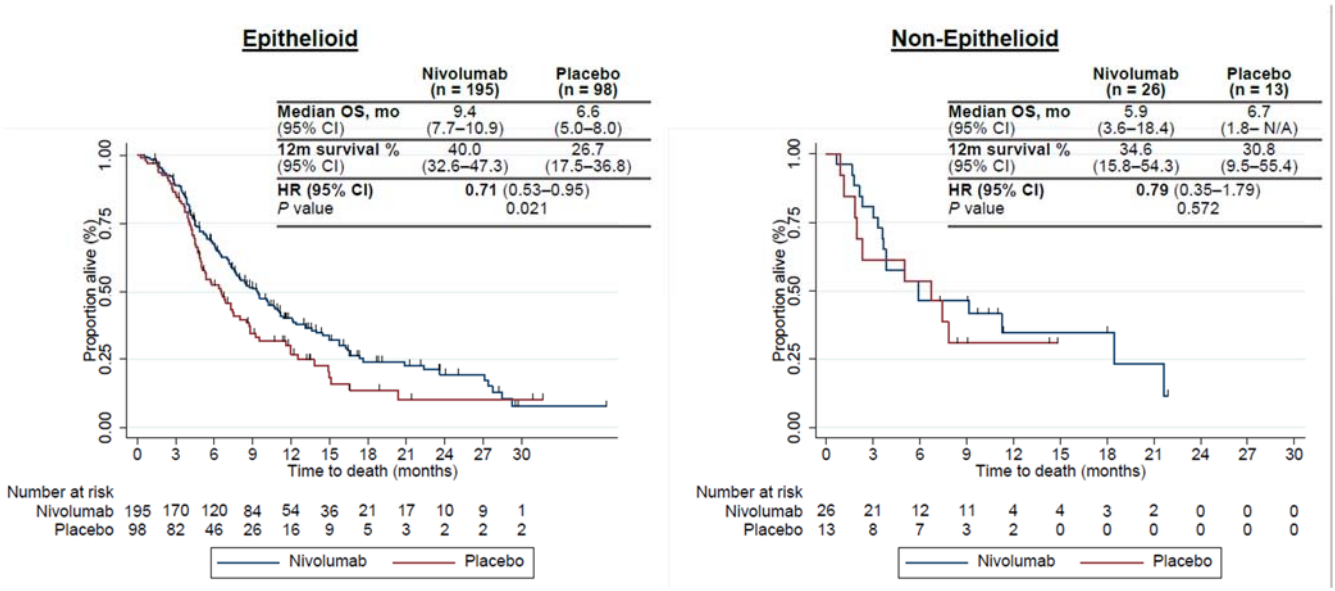
In CheckMate-743, 24.6% of subjects (n = 149) had non-epithelioid tumour histology by CRF source, which included tumours with mixed (8.9%), sarcomatoid (11.7%) or other (4.0%) histology. Assessment of outcomes by more specific non-epithelioid subgroups (mixed, sarcomatoid and other) was limited by the small patient numbers in each non-epithelioid subtype, and formal statistical analyses were not done. Please also note that histology subtyping in CheckMate-743 was not assessed by central review, but instead was investigator-assessed and recorded on the CRF.

In real-life clinical practice in the UK, a high proportion of patients with MPM have unknown or not otherwise specified (NOS) histology. Real-world data from the CAS registry in England from January 2013-December 2017 showed that of 2,810 patients who received first-line pemetrexed + platinum-based therapy, 34.5% had histology that was not otherwise specified and 3.2% were unknown subtype.[2] Reasons given for this by UK clinical experts were the technical difficulties with obtaining a biopsy in MPM and that histological subtype can be a broad spectrum that is hard to define (Appendix N).

In CheckMate-743, the treatment effect of nivolumab + ipilimumab versus PDC was consistent across histological subtypes. The survival benefit with PDC was as expected in each subgroup, so that the magnitude of effect was greater in the non-epithelioid subgroup than in the epithelioid subgroup. However, the greater treatment

effect of immunotherapy with the non-epithelioid subtype was not observed in CONFIRM, a recent RCT that compared nivolumab monotherapy with placebo for the second-line treatment for MPM. Contrary to CheckMate-743, results from CONFIRM showed a greater treatment effect in the epithelioid subgroup than in the non-epithelioid subgroup (Figure 3).[14]

Figure 3. CONFIRM: overall survival by histology



Source: Fennell[14]

For these reasons, the company considers the outcomes in the histological subgroups in CheckMate-743 as descriptive in nature and should be interpreted with caution. In addition, the company does not consider patient selection criteria for nivolumab + ipilimumab by histological subtype as appropriate, given the limitations in histological subtyping in real-life clinical practice; the significant OS benefit seen in both epithelioid and non-epithelioid subgroups in CheckMate-743 and the high clinical unmet need of all patients with unresectable MPM eligible for SACT.

A12. Regarding the risk of bias/methodological quality assessment for the CheckMate-743 trial: Table 12 in the CS reports the answer for 'Was randomisation carried out appropriately?' as 'Yes/No. Please clarify what was the intended response for this question.

This was a formatting error in the company submission and should read 'Yes': CheckMate-743 was assessed as having a low risk of bias due to randomisation as random numbers were generated by a computer/web-based response system.

A13. Priority question. Please provide estimates with p values of the independent effects (interaction terms) of each of PD-L1 status and histological subtype on the treatment effects (HRs) of nivolumab + ipilimumab vs. PDC on OS and PFS.

As explained in responses to A10 and A11, patient and event numbers in the PD-L1 and non-epithelioid subgroups were small, not prespecified and not powered; therefore, any statistical analyses in the subgroups are descriptive in nature and should be interpreted with caution. As such, the test for interaction requested was not reported for CheckMate-743.

A14. Priority question. Please provide the following numbers (proportions) of patients (and average number of cycles per patient) in the PDC arm:

i. Those who received only cisplatin

ii. Those who received only carboplatin

iii. Those who began on cisplatin and switched to carboplatin, analysed by reason for switch

iv. Those who began on carboplatin and switched to cisplatin, analysed by reason for switch

Table 9. Treatment received in the PDC arm

Treatment in PDC arm	N (%)
Those who received only cisplatin	75 (26.4%)
Those who received only carboplatin	180 (63.4%)
Those who began on cisplatin and switched to carboplatin	29 (10.2%)
Those who began on carboplatin and switched to cisplatin	0

Source: Bristol-Myers Squibb[12]

The choice of cisplatin or carboplatin in CheckMate-743 was according to the investigator. Switching from cisplatin to carboplatin and vice versa was allowed per protocol, and reasons were reported in the CRF. If switching was due to toxicity, the other study drug was continued for the remainder of the cycles. In CM-743, 284 participants received up to 6 cycles of PDC with pemetrexed in combination with either carboplatin or cisplatin and treatment received in the PDC arm is shown in Table 9 above. Overall, 100% of the 284 participants of the PDC arm received a dose of pemetrexed, while 74% (209 of 284) of the PDC arm received a dose of

carboplatin and 37% (104 of 284) received a dose of cisplatin. Only 10.2% of patients (29 of 284) switched from cisplatin to carboplatin after the first dose due to the investigator's decision. Median number of doses of cisplatin was 5.0 (IQR 3.0–6.0), of carboplatin was 6.0 (4.0–6.0), and of pemetrexed was 6.0 (4.0–6.0). Since carboplatin and cisplatin have been shown in studies to be clinically equivalent in MPM (see response to A4), the effect of switching is not expected to have any clinically relevant impact on outcomes.

A15. Priority question. Please provide the numbers of patients who experienced each all-cause/treatment emergent Grade 3-4 adverse event for each arm of the trial where the percentage experiencing the event was at least 1%.

Rates of grade 3 or 4 treatment-related adverse events from CheckMate-743 were published in the supplementary appendix of Baas et al.[6] and reproduced in Table 10 below. Rates of grade 3 or 4 all-cause adverse events from CheckMate-743[12] are presented in Table 11.

Table 10. Treatment-related adverse events of grade 3 or 4 severity (≥ 1%)

	Nivolumab + ipilimumab (n = 300)		PDC (n = 284)	
Event, n (%)	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Any TRAE	79 (26.3%)	12 (4.0%)	73 (25.7%)	18 (6.3%)
≥ 1% of patients in any treatment group				
Increased lipase	11 (3.7%)	2 (0.7%)	1 (0.4%)	0
Diarrhoea	10 (3.3%)	0	2 (0.7%)	0
Colitis	7 (2.3%)	0	1 (0.4%)	0
Increased amylase	6 (2.0%)	1 (0.3%)	0	0
Acute kidney injury	4 (1.3%)	0	0	0
Increased alanine aminotransferase	3 (1.0%)	2 (0.7%)	0	0
Abnormal hepatic function	3 (1.0%)	2 (0.7%)	0	0
Fatigue	3 (1.0%)	0	5 (1.8%)	0
Pruritus	3 (1.0%)	0	0	0
Rash	3 (1.0%)	0	0	0
Increased aspartate aminotransferase	3 (1.0%)	0	0	0
Infusion-related reaction	3 (1.0%)	0	0	0
Hypopituitarism	3 (1.0%)	0	0	0
Thrombocytopenia	2 (0.7%)	0	4 (1.4%)	6 (2.1%)
Anaemia	1 (0.3%)	0	32 (11.3%)	0
Neutropenia	1 (0.3%)	1 (0.3%)	31 (10.9%)	12 (4.2%)

	Nivolumab + ipilimumab (n = 300)		PDC (n = 284)	
Event, n (%)	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Nausea	1 (0.3%)	0	7 (2.5%)	0
Asthenia	0	0	12 (4.2%)	0
Vomiting	0	0	6 (2.1%)	0
Leukopenia	0	0	5 (1.8%)	3 (1.1%)
Pancytopenia	0	0	1 (0.4%)	4 (1.4%)

TRAE = treatment-related adverse event
Included events reported between the first dose of study drug and 30 days after the last dose of study drug.
Source: Baas et al.[6]

Table 11. All-cause adverse events of grade 3 or 4 severity (≥ 1%)

	Nivolumab + ipilimumab (n = 300)	PDC (n = 284)
Event, n (%)	**Grade 3-4**	**Grade 3-4**
Total subjects with an event	159 (53.0)	121 (42.6)
≥ 1% of patients in any treatment group		
General disorders and administration site conditions	29 (9.7)	30 (10.6)
Fatigue	9 (3.0)	5 (1.8)
Pyrexia	4 (1.3)	2 (0.7)
Asthenia	4 (1.3)	12 (4.2)
Oedema peripheral	0	0
Non-cardiac chest pain	(1.7)	1 (0.4)
Chest pain	4 (1.3)	3 (1.1)
Pain	0	2 (0.7)
Malaise	2 (0.7)	0
Mucosal inflammation	0	2 (0.7)
Peripheral swelling	0	
General physical health deterioration	0	3 (1.1)
Gastrointestinal disorders	28 (9.3)	21 (7.4)
Diarrhoea	12 (4.0)	2 (0.7)
Nausea	2 (0.7)	7 (2.5)
Constipation	1 (0.3)	2 (0.7)
Vomiting	0	6 (2.1)
Abdominal pain	2 (0.7)	2 (0.7)
Colitis	7 (2.3)	1 (0.4)
Respiratory disorders	27 (9.0)	17 (6.0)
Dyspnoea	7 (2.3)	9 (3.2) 0
Cough	2 (0.7)	0
Pleural effusion	3 (1.0)	2 (0.7)
Pneumonitis	3 (1.0)	0
Hiccups	0	0
Pulmonary embolism	3 (1.0)	3 (1.1)

Event, n (%)	Nivolumab + ipilimumab (n = 300) Grade 3-4	PDC (n = 284) Grade 3-4
Skin and tissue disorders	12 (4.0)	1 (0.4)
Pruritus	3 (1.0)	0
Rash	3 (1.0)	0
Rash maculo-papular	2 (0.7)	0
Dry skin	0	0
Infections and infestations	25 (8.3)	12 (4.2)
Nasopharyngitis	1 (0.3)	0
Pneumonia	8 (2.7)	5 (1.8)
Lower respiratory tract infection	3 (1.0)	1 (0.4)
Metabolism and nutrition disorders	22 (7.3)	21 (7.4)
Decreased appetite	3 (1.0)	4 (1.4)
Hypoalbuminaemia	1 (0.3)	2 (0.7)
Hyponatraemia	5 (1.7)	4 (1.4)
Dehydration	3 (1.0)	2 (0.7)
Hypokalaemia	0	3 (1.1)
Musculoskeletal and connective tissue disorders	13 (4.3)	2 (0.7)
Arthralgia	3 (1.0)	0
Myalgia	0	0
Back pain	2 (0.7)	1 (0.4)
Pain in extremity	0	0
Musculoskeletal pain	2 (0.7)	0
Investigations	32 (10.7)	9 (3.2)
Blood creatinine increased	1 (0.3)	0
Lipase increased	16 (5.3)	1 (0.4)
Amylase increased	9 (3.0)	1 (0.4)
Alanine aminotransferase increased	6 (2.0)	0
Blood alkaline phosphatase increased	2 (0.7)	0
Weight decreased	0	1 (0.4)
Aspartate aminotransferase increased	5 (1.7)	0
Nervous system disorders	15 (5.0)	2 (0.7)
Headache	0	0
Dizziness	0	0
Dysgeusia	0	0
Syncope	4 (1.3)	1 (0.4)
Blood and lymphatic system disorders	18 (6.0)	84 (29.6)
Anaemia	8 (2.7)	39 (13.7)
Neutropenia	3 (1.0)	45 (15.8)
Thrombocytopenia	2 (0.7)	11 (3.9)
Leukopenia	0	8 (2.8)
Pancytopenia	0	5 (1.8)

Event, n (%)	Nivolumab + ipilimumab (n = 300) Grade 3-4	PDC (n = 284) Grade 3-4
Febrile neutropenia	0	3 (1.1)
Endocrine disorders	5 (1.7)	0
Hypothyroidism	0	0
Hypopituitarism	3 (1.0)	0
Psychiatric disorders	2 (0.7)	2 (0.7)
Insomnia	0	0
Anxiety	0	0
Injury, poisoning and procedural complications	7 (2.3)	2 (0.7)
Infusion related reaction	4 (1.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (4.0)	5 (1.8)
Malignant neoplasm progression	9 (3.0)	5 (1.8)
Cardiac disorders	10 (3.3)	5 (1.8)
Atrial fibrillation	2 (0.7)	3 (1.1)
Vascular disorders	12 (4.0)	1 (0.4)
Hypertension	6 (2.0)	1 (0.4)
Hepatobiliary disorders	17 (5.7)	0
Hepatic function abnormal	5 (1.7)	0
Immune-mediated hepatitis	3 (1.0)	0
Renal and urinary disorders	9 (3.0)	2 (0.7)
Acute kidney injury	5 (1.7)	0

Included events reported between the first dose of study drug and 30 days after the last dose of study drug.
Source: Bristol-Myers Squibb[12]

A16. Priority question. According to Table 6.5.3-1 in the CSR, nearly half of all patients received subsequent therapy.

a. Please explain the differences between the two arms in the choice of subsequent therapy and discuss the likely implications of these differences on the relative effectiveness of nivolumab + ipilimumab vs. PDC.

After study treatment was discontinued, similar proportions of patients in each treatment arm received subsequent therapy: 44.2% of those treated with nivolumab + ipilimumab subjects and 40.7% of those treated with PDC. Most subjects received subsequent chemotherapy (43.2% and 31.5% from the nivolumab + ipilimumab and PDC arms, respectively). Subsequent immunotherapy (anti PD-1/PD-L1, anti-CTLA-

4, other) was received by 3.3% of the nivolumab + ipilimumab and 20.2% of the PDC arm, respectively. A small percentage of subjects received subsequent experimental therapies (0.7% and 4.0% in the nivolumab + ipilimumab and PDC arms, respectively).

In CheckMate-743, more patients received subsequent immunotherapy after PDC than with nivolumab + ipilimumab, which is expected since use of a subsequent therapy with a different mode of action to prior treatment is standard clinical practice.

Patients with MPM treated with second-line therapies have a short life expectancy, and therefore duration of subsequent treatments is also short. Real-world data from the CAS registry of patients with unresectable MPM in England from January 2013-December 2017 showed that median OS was 8.5 months from start of second-line therapy and median treatment duration of second-line therapy was 1.6 months.[2] Due to the short duration of subsequent therapies, no significant differences in survival outcomes are anticipated as a result of any differences in subsequent therapy in CheckMate-743. This assumption was validated by UK clinical experts (Appendix N). There are currently no second-line therapies licensed for use in MPM as no second-line therapy has shown a survival benefit in MPM in a randomised controlled trial with an active comparator.

Overall, the company considers that the potential for the assessment of OS to be confounded by subsequent treatments to be low and any confounding is likely to be biased in favour of the PDC arm, resulting in an underestimate of the incremental improvement in OS reported for nivolumab + ipilimumab.

b. Please provide evidence that the types of subsequent therapy in the trial are those that would also be used in England NHS practice or, if this is not the case, please discuss the likely implications of any discrepancy.

There is no standard second-line therapy in MPM used in NHS clinical practice, which was confirmed by UK clinical experts (Appendix N). Second-line treatment options are not well defined because there is no second-line therapy approved for use, and therapies undergoing clinical trials are recommended above any other option according to the British Thoracic Society guidelines.[3] This is supported by

real-world data from the CAS registry of patients with unresectable MPM in England from January 2013-December 2017. Results showed that among 3,159 patients who received first-line therapy, 784 (25.2%) received a second-line therapy during the study period: of these, 43.6% received second-line PDC (platinum + pemetrexed), 18.6% received second-line treatment in a clinical trial, and 24.1% received second-line vinorelbine.[2] Supportive evidence is provided by a real-world cross-sectional study on treatment patterns in Europe, which included 248 patients from the UK. In the UK in 2019, [redacted].[5]

Although rates of second-line therapy in CheckMate-743 are higher than those reported in real-life NHS practice in the CAS registry and the EU cross-sectional study, the types and duration of subsequent therapy in CheckMate-743 are likely to reflect NHS practice by treatment arm.

In CheckMate-743, subsequent immunotherapy was used in 20.2% of patients treated with PDC, which is in line with the current NHS practice during the COVID-19 pandemic. During the COVID-19 pandemic, there is the option to give patients with MPM second-line nivolumab monotherapy in the NHS in England instead of second-line chemotherapy to reduce the risk of immunosuppression.[15] UK clinical experts confirmed that second-line nivolumab monotherapy was being used in NHS clinical practice currently.

In CheckMate-743, subsequent chemotherapy was used in 43.2% of patients treated with nivolumab + ipilimumab, which is in line with the expected change in the treatment pathway in NHS practice. As nivolumab + ipilimumab is expected to replace PDC as current first-line standard of care, it is anticipated that PDC would become the new standard second-line therapy, which was confirmed by UK clinical experts.

A17. It is stated in Appendix E that “The CRF did not have an option for treatment discontinuation due to subjects completing the maximum duration of treatment per protocol (2 years of nivolumab + ipilimumab or 6 cycles of chemotherapy); therefore, this action was captured as “not reported” on the CRF as reason for treatment discontinuation…of the 189 chemotherapy-treated subjects with reason off treatment

"not reported", 176 (93.1%) subjects did receive all 6 cycles (the maximum allowed duration of chemotherapy per protocol)."

a. Please clarify if this means that 93.1% of patients discontinued nivolumab + ipilimumab at 2 years. If not, then how many (what proportion) did?

No. The 93.1% refers to the proportion of the 189 patients treated with PDC captured as 'not reported' in the CRF who had actually received 6 cycles of PDC per protocol, as shown in Table 12 of Document C (Appendix E, p40). Most subjects discontinuing treatment for reason 'not reported', had actually completed treatment per protocol, as the CRF did not have an option for treatment discontinuation due to subjects completing the maximum duration of treatment per protocol (2 years of nivolumab + ipilimumab or 6 cycles of chemotherapy).

For nivolumab + ipilimumab, 98.3% of patients (n = 295) had discontinued therapy at any timepoint up to the end of the 2-year treatment period, with only 5 patients still on treatment at the time of the database lock. Of the 295 patients who discontinued treatment, 18 patients in the CRF were reported as completing the maximum 2 years treatment for nivolumab + ipilimumab and discontinuing at 2 years: 6 classed as 'other', 3 classed as 'not reported', 7 classed as 'maximum clinical benefit' and 2 as 'administrative reason by the sponsor'.

The maximum duration of treatment per protocol was 2 years for nivolumab + ipilimumab. Most patients in both treatment arms received ≥ 90% of planned doses (see Table 16, p60 of Document B) and 23.7% of subjects received more than 12 months of nivolumab + ipilimumab treatment. As of the database lock for the interim analysis on 3 April 2020 (median follow up, 29.7 months), 98.3% of subjects in the nivolumab + ipilimumab arm and 100% of subjects in the PDC arm had discontinued treatment. The main reason for treatment discontinuation in the nivolumab + ipilimumab arm was disease progression (60.7%, vs. 15.5% in the PDC arm). A higher proportion of subjects in the nivolumab + ipilimumab arm than in the PDC arm discontinued study therapy owing to study drug toxicity (19.7% vs. 8.5%). However, the median duration of treatment was longer in the nivolumab + ipilimumab arm versus the PDC arm (5.55 months vs. 3.48 months, respectively).

b. Please explain what is meant, as reported in Table 12, by: ”Maximum clinical benefit”?

One of the options in the CRF for discontinuing treatment was “maximum clinical benefit” as assessed by the investigator or the patient. Investigators are guided to select this reason if the investigator has determined that the subject will not benefit from further study treatment. This was the reason given for 12 patients (2.1%) of the CheckMate-743 study population (3.3% in the nivolumab + ipilimumab arm and 0.7% in the PDC arm). Some of these patients may have reached the maximum duration of treatment per protocol, as the CRF did not have an option for treatment discontinuation due to subjects completing the maximum duration of treatment per protocol (2 years of nivolumab + ipilimumab or 6 cycles of chemotherapy), as explained in A17a above.

End of life criteria

A18. Priority question. Section B.2.1.3.3 of the CS states that nivolumab + ipilimumab fulfils the NICE end of life criteria in all patients with unresectable MPM. Please confirm that the data presented, on the survival benefit with nivolumab + ipilimumab versus PDC, are for patients with ECOG PS 0-1 only.

Yes. The data presented on the survival benefit with nivolumab + ipilimumab is for all patients with unresectable MPM eligible for systemic anticancer treatment, which is patients with ECOG PS0-1, which is the patient population in the CheckMate-743 trial.

Section B: Clarification on cost-effectiveness data

Cost effectiveness review

While reviewing the clarification questions, two data errors were identified in the submitted model:

- One drug-related adverse event occurring in ≥ 2% of patients was omitted (see response to question B11, part a)
- The proportions of cisplatin and carboplatin use in combination with pemetrexed were incorrect (see response to question B14, part a)

These two corrections have been made to the model in the revised base case, which is used for all scenario analyses presented in section B. The revised base case results are presented in Table 12 below. The ICER increased from £77,502 to £77,531.

Table 12. Revised base-case incremental results of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin in first-line unresectable MPM

Technologies	Total costs (£)	Total LYGs	Total QALYs	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per QALY, £
Submitted base-case results							
Nivolumab + ipilimumab	xxxxxx	xxxxxx	xxxxxx				
Pemetrexed + cisplatin or carboplatin	xxxxxx	xxxxxx	xxxxxx	54,397	0.916	0.702	77,502
Revised base-case results							
Nivolumab + ipilimumab	xxxxxx	xxxxxx	xxxxxx				
Pemetrexed + cisplatin or carboplatin	xxxxxx	xxxxxx	xxxxxx	54,417	0.916	0.702	77,531

Inc = Incremental; LYG = life-year gained; QALY = quality-adjusted life-year.

B1. Inclusion criteria for the cost effectiveness review are provided in Figures 6, 8 and 9 in Appendix H, I and J, respectively.

a. Please provide justification for the inclusion criteria “Line of treatment unclear”, “No SGA disease” and “No SGA LOT”.

b. Please discuss whether any potentially relevant publications for cross-validation may have been missed because of these criteria, which resulted in the exclusion of numerous articles.

The cost-effectiveness review focused on identifying relevant publications conducted in the first line MPM setting with appropriate economic outcomes reported. However, we included the studies with "LOT unclear," "No SGA disease," and "No SGA LOT" only at the first screening stage based on titles and abstracts. There were publications in which authors did not sufficiently report the details related to "LOT" or

"disease." Therefore, based on the uncertainty principle, we initially included these publications.

After the detailed evaluation of full-texts, these studies were observed to report data not aligned with our PICOS, e.g., mixed cancer data reported, not specific to mesothelioma (excluded on "no SGA disease"); mixed data for different LOTs, not specific to 1st line (excluded on "no SGA LOT"); lack of information on primary/prior treatment status to accurately label the LOT (excluded on "LOT unclear").

However, we ensured the inclusion of all the relevant full economic evaluations (e.g., cost-effectiveness/cost-utility/cost-benefit-analyses) and partial economic evaluations (like cost-of-illness studies or budget impact analyses). None of the publications relevant to the 1st line MPM setting were missed in the systematic review. We validated the results of this review with some of the previously published findings/reviews/HTA reports[16-19] and found no additional relevant publications.

Intervention & comparators

B2. Priority question. The model does not include BSC or raltitrexed as comparators, but these were identified as relevant comparators in the NICE scope. Full incremental analyses should be provided where there is more than one comparator.

a. Conditional on your response to A1, please include BSC as a comparator in the model and provide a full incremental analysis.

b. Conditional on your response to A2, please include raltitrexed as a comparator in the model and provide a full incremental analysis.

c. Conditional on your response to A3, please provide a full incremental analysis treating pemetrexed + cisplatin and pemetrexed + carboplatin as separate comparators.

Please see responses to questions A1-A3. No updates have been made to the model given that these comparators are not considered clinically relevant.

Population

B3. Priority question. No subgroup analyses are provided. The NICE scope identified histologic subtype (epithelioid, sarcomatoid, biphasic) and level of PD-L1 expression as relevant subgroups.

a. Please provide subgroup analyses for these two subgroups and the model file with these subgroup analyses included. Please provide detail on whether relevant tests for both subgroups are routinely performed in this population in England NHS practice, and if not, please incorporate the cost of relevant tests required in the modelling.

As described in responses to questions A10 and A11, the company considers the clinical data that was presented in the CS for the histological and PD-L1 subgroups in CheckMate-743 as descriptive in nature and should be interpreted with caution. The median OS benefit of nivolumab + ipilimumab was consistent across histological subtypes, and the magnitude of effect differences were driven by the known difference in PDC performance between these subtypes. In addition, a high proportion of patients with MPM in real-life clinical practice in the UK have unknown or not otherwise specified (NOS) histology, while PD-L1 testing is not standardised and not an established predictive biomarker in MPM. As such, the company does not consider economic modelling of nivolumab + ipilimumab by histological subtype or PD-L1 expression as appropriate, given the high clinical unmet need of all patients with unresectable MPM eligible for SACT and the OS benefit seen in all subgroups in CheckMate-743.

Model structure and assumptions

B4. NICE Decision Support Unit (DSU) technical support document (TSD) 19 recommended the use of state transition models (STMs) alongside partitioned survival models (PSMs) to verify the plausibility of PSM extrapolations and explore key clinical uncertainties in the extrapolation period.

a. Please justify the use of a PSM given the issues highlighted in NICE DSU TSD 19, particularly regarding the extrapolation of PFS and OS while assuming structural independence between these endpoints.

b. Please use state transition modelling to assist in verifying the plausibility of the PSM extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11).

Multiple model structures were considered during the development of the economic model, including Markov modelling. However, based on input from health economic advisory boards and to be aligned with previous NICE appraisals,[18,20] a partitioned survival model was chosen. A virtual European advisory board for the economic modelling of nivolumab + ipilimumab in 1L MPM was carried out in November 2020 and consisted of 12 experts across Europe, including 4 from the UK (one clinical oncologist, one clinical senior lecturer, one professor of medical statistics and one senior research fellow). Advisors agreed that partitioned survival models (PSM) were widely accepted by HTA bodies due to their straightforward approach and their use of data taken directly from the trials (OS and PFS); and most advisors agreed with a PSM being used for nivolumab + ipilimumab in 1L MPM. CheckMate-743 has sufficient follow up for OS to justify a PSM approach (with 22.1 months minimum follow up and further data cuts expected). Markov models allow for greater flexibility with regards to assumptions and model inputs, and potentially allow for exploration of the impact of subsequent treatments on OS in finer detail. However, Markov models are more 'data hungry' and post-progression data to populate a model are limited in this instance. It is unlikely that this would have a large impact on outcomes as post-progression treatments are administered for a short duration in this indication. As a general response to this question, it is also important to note that state transition models per se do not necessarily result in different results compared to PSM. As shown by Briggs et al.[21], a state transition model utilising the same underlying data as a PSM and relaxing the Markovian assumption allowing for time dependency resulted in very similar outcomes.

Treatment effectiveness

B5. Priority question. Please provide clarification regarding the piecewise approach to estimate OS, using Kaplan-Meier estimates up to the break point of 22 months and extrapolation using parametric survival models after this point.

a. Based on the economic model it appears that a piecewise model (Kaplan-Meier estimates + loglogistic distribution) was used for nivolumab +

ipilimumab. This is not described nor justified in the CS. Please clarify and justify the approach used to estimate OS for nivolumab + ipilimumab.

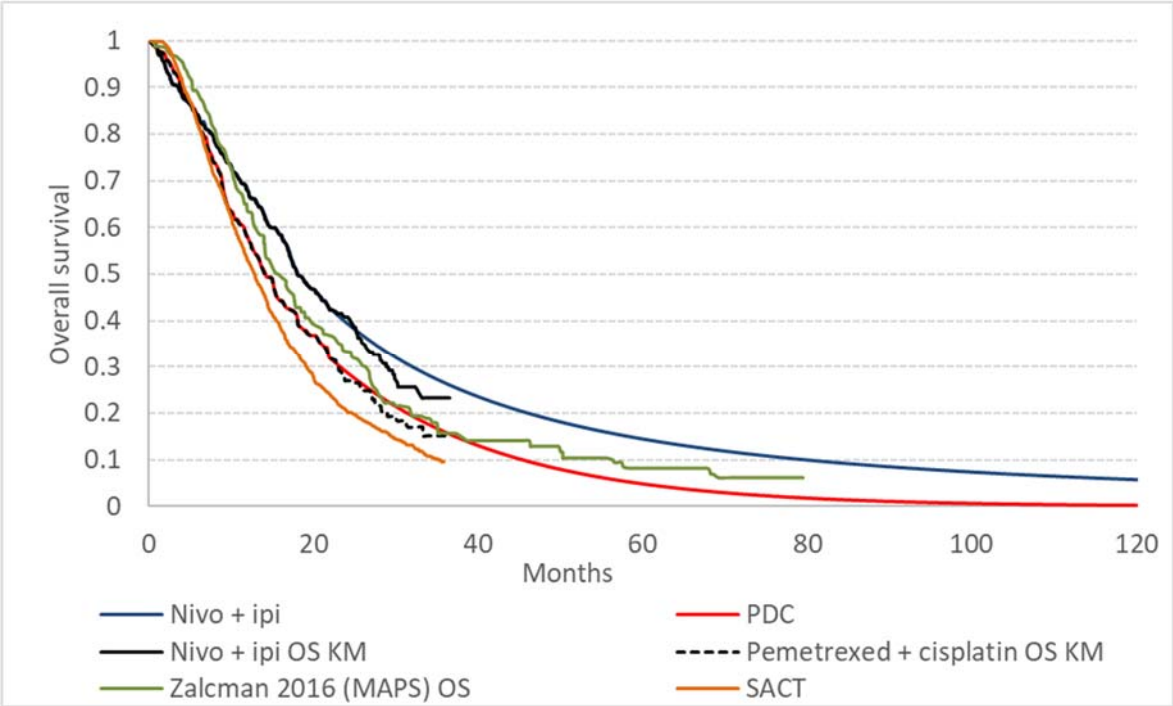
It is correct that a piecewise model was used in the base-case for both nivolumab + ipilimumab and for the PDC arm, and we acknowledge that the rationale provided in the CS could be misinterpreted as the piecewise model being only applicable to the PDC arm. The decision to utilise a piecewise model was primarily guided by the PDC arm. As presented in the CS, distributions with the best statistical and visual fit to the KM data for the PDC arm did not provide plausible long-term extrapolations. The chosen base-case distribution for PDC (exponential) provided the most plausible long-term extrapolation that was aligned with clinical expert input but had a relatively poor fit to the within-trial data (underestimating within-trial survival). Thus, to overcome this limitation for the within-trial period the piecewise approach was selected. The same issue of fit to the within-trial data was not seen to the same extent in the nivolumab + ipilimumab arm. However, for consistency the approach was applied to both arms in the model. The use of a piecewise approach was considered to be conservative because the parametric curves underestimated the within-trial survival for the PDC arm before the break point. The use of a piecewise approach thus resulted in a slightly increased ICER when compared to the use of fully parametric models.

b. Please provide a figure plotting the survival estimates using the selected approach to estimate OS in the CS base-case (presumably the piecewise approach was used for both PDC [with exponential distribution] and for nivolumab + ipilimumab [with log-logistic distribution]) as well as Kaplan-Meier estimates using the Checkmate 743 data (curves for both PDC and nivolumab + ipilimumab), the MAPS data and the SACT data. Please add the number of patients at risk per 3 months (separately per curve) as well as for the 22 months break point to the x-axis.

The base-case extrapolations (piecewise log-logistic for nivolumab + ipilimumab and piecewise exponential for PDC) are presented together with KM data from CheckMate-743, the digitized KM curves for the PDC arm of the MAPS trial,[22] and the SACT data from Baas et al.[6] in Figure 4, as requested. No patient at-risk information was available for the SACT data and it was only reported per 20 months

for the MAPS data; therefore, it could not be included per 3 months as requested. The number of patients at risk in CheckMate-743 per 3 months was reported in the CS but has also been presented in Table 13 below.

Figure 4. Base case distributions overlaying the CheckMate-743, SACT and MAPS Kaplan-Meier data



MAPS data based on digitised KM curves from Zalcman et al.[22]
SACT data based on digitised KM curves from Baas et al.[6]

Table 13. Number at risk per 3-month intervals in CheckMate-743

	Number at risk month													
	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Nivolumab + ipilimumab	303	273	251	226	200	173	143	124	101	65	30	11	2	0
PDC	302	268	233	190	162	136	113	95	62	38	20	11	1	0

c. Based on the economic model, it appears that the piecewise models are implemented using parametric survival models that are estimated from baseline (time = 0) instead of being estimated specifically from the break point (e.g. of 22 months). Please justify the approach used and provide an updated

economic model as well as scenario analyses using parametric survival models estimated from the break point to inform the piecewise model.

As presented in response to question B5a and in the CS, the rationale for utilizing piecewise models was to avoid underestimating PDC survival within the trial time horizon. The decision was not driven by the identification of a structured break point (or arbitrary as referred to in question B5e) in the data from which point parametric survival curves would be fitted. Such an approach would not be preferable in our opinion, as it would only utilize a limited amount of the data available for extrapolation. Only utilizing a proportion of the data would, as described in the NICE DSU TSD 21 and highlighted by the ERG in question B5e, result in greater uncertainty when fitting survival models.

In response to the request from the ERG, we have however performed survival analyses based on the 22 months break point. The resulting survival curves from this analysis are presented in Figure 5 and Figure 6 together with the CheckMate-743 and the MAPS KM data. Table 14 presents the statistical fit of the distributions. As can be seen in Figure 5, the distributions fitted only to the data from 22 months and beyond for nivolumab + ipilimumab resulted in a wide range of long-term survival, with all extrapolations being clinically implausible because they predict survival curves that cross those observed in the MAPS trial. Similarly, Figure 6 shows that the extrapolations for PDC resulted in several distributions that are also clinically implausible. Several of the distributions resulted in predictions with greater survival than observed in the MAPS trial, and the lognormal curve resulted in long-term survival predictions that are greater for PDC than for nivolumab + ipilimumab. Based on these findings and aligned with the ERG and the NICE DSU TSD 21, utilizing only part of the available data does not result in improved long-term predictions. Therefore, the extrapolations fitted from the 22-month break point have not been implemented in the model. Further, as can be seen in our response to question B5i, the inclusion of spline models resulted in an improved fit to the data and plausible long-term survival for the PDC arm while utilizing the full data set. Therefore, spline models provide a more robust alternative to the original piecewise model when compared to extrapolations only fitted to a subset of the data.

Figure 5. Independent models for nivolumab + ipilimumab fitted from a 22 months break point overlaying the CheckMate-743 and MAPS Kaplan-Meier data

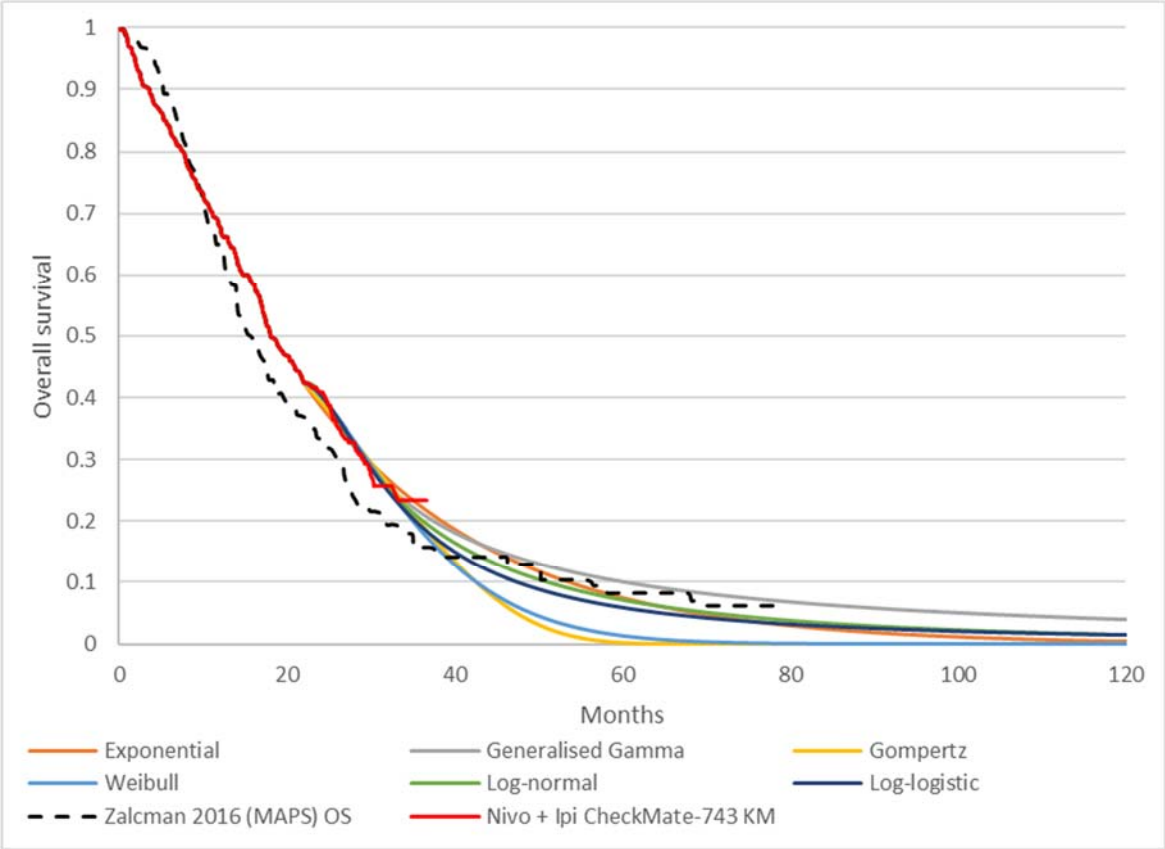


Figure 6. Independent models for PDC fitted from a 22 months break point overlaying the CheckMate-743 and MAPS Kaplan-Meier data

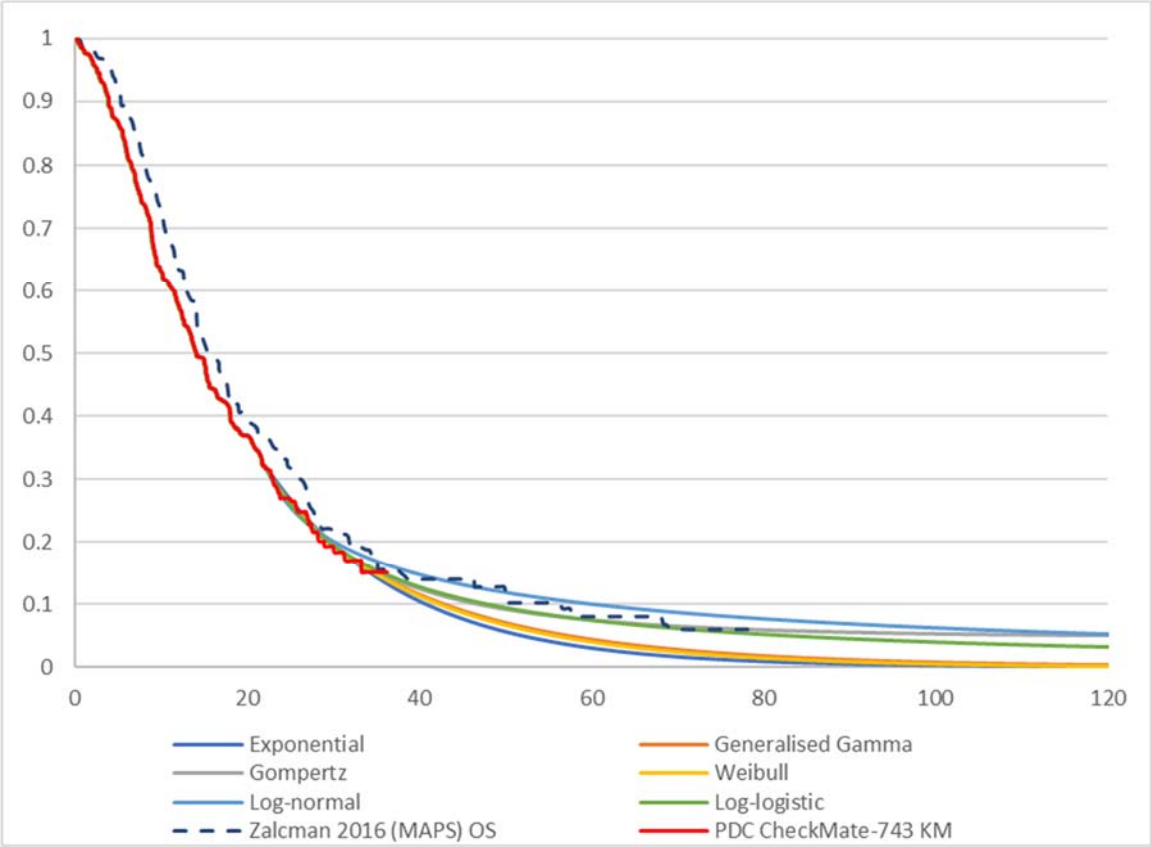


Table 14. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data from 22 months

Arm	Distribution	AIC	BIC
Nivolumab + ipilimumab	Lognormal	249.2	254.8
	Log-logistic	250.8	256.3
	Generalised gamma	250.9	259.2
	Weibull	252.6	258.2
	Exponential	255.6	258.3
	Gompertz	256.3	261.9
PDC	Exponential	213.0	215.4
	Gompertz	214.6	219.5
	Weibull	214.7	219.6
	Log-logistic	214.7	219.6
	Generalised gamma	216.7	224.0
	Lognormal	217.8	222.7

d. Please clarify how many events occurred before and after the break point of 22 months (separately for PDC and nivolumab + ipilimumab).

Table 15 provides the number of events before and after 22 months and Table 16 provides the number of censored patients before and after 22 months.

Table 15. Number of events before and after 22 months

	Number of events		
	Nivolumab + ipilimumab	PDC	Combined
Before 22 months	169	191	360
After 22 months	31	28	59
Total	200	219	419

Table 16. Number of censored patients before and after 22 months

	Number of events		
	Nivolumab + ipilimumab	PDC	Combined
Before 22 months	16	25	41
After 22 months	87	58	145
Total	103	83	186

e. As stated in NICE DSU TSD 21 on flexible methods for survival analysis: "*Where a piecewise model is fitted to a single dataset, splitting the data into sections* according *to time means that sample sizes are reduced in later segments of the curve. This is a particular issue in later sections of the curve, where patient numbers at risk may be very small and the number of observed events may be low, leading to large standard errors and uncertainty when fitting survival models. A key point is that it is the model fitted to the latest section of the curve that is used for extrapolation*". Please justify the plausibility of the (extrapolation) approach used for the estimated piecewise models, given the number of patients at risk and observed events (both per treatment) to estimate the tail.

Although the NICE DSU TSD 21 was only published in November 2020 when we neared submission, we agree with the concerns raised in the NICE DSU TSD 21 around extrapolations based on split data sets, where limited observations will be

available to inform the long-term extrapolations and thus increase uncertainty. This is also the rationale behind fitting the extrapolations in the CS to the full dataset and not only from a break point, as explained in our response to question B5c.

f. As stated in NICE DSU TSD 21 on flexible methods for survival analysis: *"the cut-points for the various intervals may be arbitrary and may importantly influence the results of an analysis"*. Please justify the selected break point (22 months) given the responses above and provide an updated economic model as well as scenario analyses assuming different break points (with the parametric survival models estimated from the specific break point).

As presented in the CS, the break point for transitioning from KM data to parametric distributions was identified based on the minimal follow up time in CheckMate-743 (22.1 months). Up until this point, the KM curve was considered mature and thus suitable to be used directly for the model. As can be seen in Table 15 (response to question B5c) most of the events in CheckMate-743 occurred before 22 months and the majority of censoring (Table 16) occurred after this timepoint. Thus, the survival beyond 22 months was considered to be best captured by the parametric functions fitted to the full dataset.

As noted in our response to question B5c, we do not believe that there is a clear rationale for how fitting piecewise models only to later parts of the data would result in more plausible extrapolations. On the contrary, we agree with the point raised by the ERG referring the to the NICE DSU TSD 21, that only utilizing a later section of the curve where patient numbers at risk may be very small and the number of observed events may be low leads to additional uncertainty when fitting survival models. From the fitted curves presented in response to question B5c, we believe that this has been shown to be the case for the current dataset. Thus, alternative break points for fitting survival analyses have not been identified based on the data and no further survival analyses than those based on the full dataset are included in the model. However, the model allows the user to select alternative points (1-22 months in 1-month increments) from when the parametric survival curves fitted to the full data set are used in the analysis. This option can be used to investigate alternative points of transitioning from the KM data to parametric functions.

g. As stated in NICE DSU TSD 21 on flexible methods for survival analysis: "*piecewise* models *may appear clinically unjustifiable and implausible, if sudden changes in hazards are modelled*". Please justify that the piecewise models are clinically justifiable and plausible in this respect.

As noted in our response to part a of this question, the implementation of a piecewise model for the CS was not based on the identification of, for example, a certain shift in the hazard function. Thus, we do not believe the critique raised in the NICE DSU TSD 21 (regarding piecewise models appearing clinically unjustifiable and implausible if sudden changes in hazards are modelled) is applicable in this case. As noted earlier, the piecewise approach was taken to improve the within trial fit of the survival curves while maintaining clinically plausible long-term extrapolations.

h. A recent paper by Klijn et al. 2021 (https://doi.org/10.1007/s40273-020-00989-1, co-authored by BMS-employees) examined the predictive accuracy over time of different extrapolation methods to estimate OS in immuno-oncology. One key point of this paper was "*Piecewise Kaplan–Meier plus exponential models significantly underestimated the survival benefit of IO monotherapy in this case study and should be discouraged for extrapolating IO monotherapy, unless robust contrary evidence for the use of this approach is presented*". Given these findings, please provide robust contrary evidence supporting the piecewise models used in the CS base-case.

We do not see a contradiction between the key findings of the paper by Klijn et al.[23] and the approach taken in the CS. As stated in the findings of the paper and by the ERG in this question, the conclusion was that a piecewise exponential model would not be suitable for IO monotherapies. This is due to the long-term benefit and resulting long-term decreasing hazards observed for IOs. To reflect this, a piecewise log-logistic distribution was used for the nivolumab + ipilimumab arm in the CS. However, the same findings have not been observed for PDC and a piecewise exponential model is used in the CS.

i. Spline models could provide an alternative approach to the piecewise models to estimate OS. Please explore the use of spline-based models for OS (e.g.

using the flexsurvspline() function in R), including 1 and 2 knot models (with default knot location) using the hazard, odds as wells as normal scales (resulting in 6 models). Please elaborate on the appropriateness of these spline models and provide an updated economic model as well as scenario analyses using these spline models.

Spline models have been fitted to the data using the flexsurvspline() function in R with up to 2 knots, as requested. The output of the analyses has been incorporated into the economic model. The statistical fit of each distribution is presented in Table 17.

Table 17. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric spline models fitted to overall survival data

Arm	Distribution	AIC	BIC
Nivolumab + ipilimumab	Spline on hazards 1 knot	1705.2	1716.4
	Spline on probit link of survival 2 knots	1705.8	1720.6
	Spline on odds 2 knots	1706.4	1721.2
	Spline on hazards 2 knots	1706.5	1721.4
	Spline on probit link of survival 1 knot	1707.8	1718.9
	Spline on odds 1 knot	1708.7	1719.9
PDC	Spline on odds 1 knot	1737.8	1748.9
	Spline on probit link of survival 1 knot	1737.9	1749.0
	Spline on hazards 1 knot	1738.8	1749.9
	Spline on probit link of survival 2 knots	1739.3	1754.1
	Spline on hazards 2 knots	1739.7	1754.5
	Spline on odds 2 knots	1739.7	1754.5

Figure 7 and Figure 8 show the spline models fitted to CheckMate-743 overlayed with the CheckMate-743 and MAPS KM data, for nivolumab + ipilimumab and PDC respectively.

Figure 7. Independent spline models for nivolumab + ipilimumab overlaying the CheckMate-743 and MAPS Kaplan-Meier data

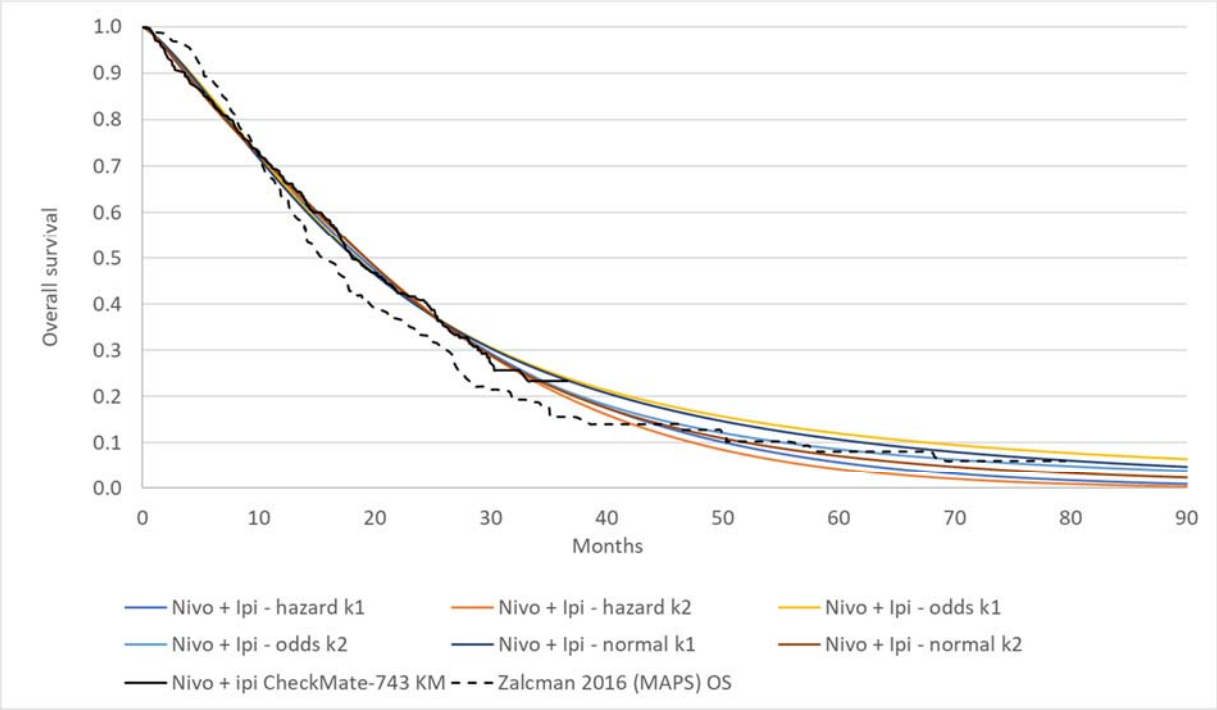
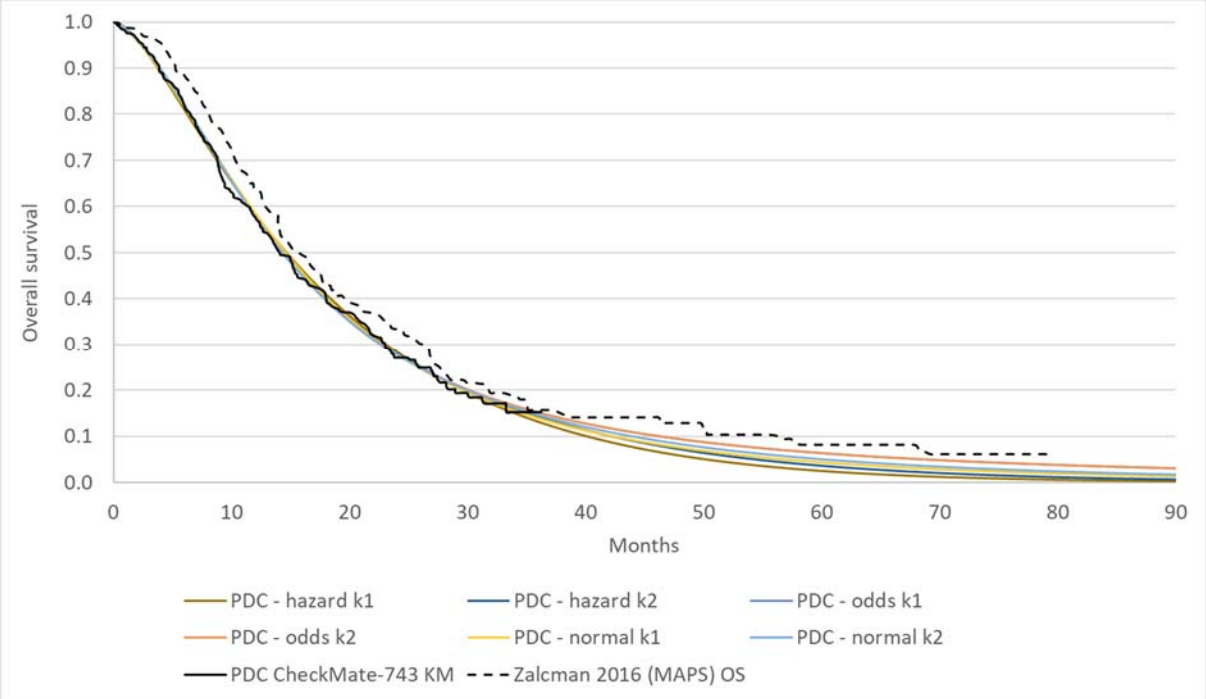


Figure 8. Independent spline models for PDC overlaying the CheckMate-743 and MAPS Kaplan-Meier data



As can be seen in the figures, the spline models provide a good visual fit to the KM data, particularly for the PDC arm. For the nivolumab + ipilimumab arm, all distributions except the spline 1 knot odds resulted in curves crossing the PDC arm of MAPS data, so were considered clinically implausible based on heuristics provided in the CS. The spline 1 knot odds predicted survival just above the PDC arm from MAPS, and was thus also considered to provide long term survival lower than clinically expected.

For PDC, the clinical experts consulted during the development of the CS considered that rates of 5-year, 7.5-year and 10-year survival for PDC patients would be 5%, 2% and 0%, respectively. They also considered that the log-logistic extrapolations were probably be too optimistic, whereas the generalised gamma were too pessimistic, predicting 5-year OS at 8% and 3%, respectively. Based on this, the exponential was considered to be the most appropriate distribution for estimating long term survival with 5% alive at 5 years, 1% at 7.5 years, and 0% at 10 years. Reviewing the spline models considering this, spline 1 knot hazard and spline 1 and 2 knots odds would not be appropriate (resulting in 3%, 6% and 6% survival at 5 years, respectively, and with patients surviving until 15 years with spline 1 and 2 knots odds). However, spline 2 knots hazard and spline 1 and 2 knots normal resulted in clinically plausible long-term survival. Spline 2 knots might be seen to be on the high end, and 2 knots hazards on the lower end for 5- and 10-year survival. Given the good within-trial fit of these models compared to the exponential model, they could be considered a valid alternative to the piecewise approach. Thus, scenarios without piecewise modelling for both arms have been presented below with loglogistic used for modelling nivolumab + ipilimumab and spline 2 knots hazard, spline 1 knot normal, and 2 knots normal used for PDC. As can be seen from the results presented in Table 18, spline 2 knots hazard and spline 1 knot normal result in a slightly lower ICER compared to the original company base case; whereas, spline 2 knots normal increases the ICER slightly.

Table 18. Results of scenario analyses for alternative spline distributions for PDC OS

Scenario	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per LYG, £	Incremental costs per QALY, £	Difference from the base case (£, QALY)
Base case	xxxxxx	xxxxxx	xxxxxx	59,439	77,531	

Scenario	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per LYG, £	Incremental costs per QALY, £	Difference from the base case (£, QALY)
Spline 2 knots hazard	xxxxxx	xxxxxx	xxxxxx	55,597	73,755	-3,776
Spline 1 knot normal	xxxxxx	xxxxxx	xxxxxx	57,957	76,149	-1,383
Spline 2 knots normal	xxxxxx	xxxxxx	xxxxxx	60,191	78,291	760

Inc = incremental; LY = life-year; LYG = life-year gained; QALY = quality-adjusted life-year.

j. Please provide data/evidence (e.g. based on MAPS or SACT data) as well as expert opinion to validate the long-term OS extrapolations (e.g. based on CS Tables 29 and 31).

There is a paucity of long-term survival data available for patients with MPM. Clinical input was sought, and advisory boards held in preparation for our submission and the data provided for validation within the CS are considered the most clinically relevant to use. In particular, the MAPS data[22] were considered highly relevant with the longest follow up in a similar patient population. The MAPS data have thus been used in the CS for curve selection, for example in Figure 35 and Figure 36. Further, the clinicians who were consulted confirmed that the selected distributions would result in the most plausible long-term extrapolations.

B6. CS Figure 28 is very informative to examine the smoothed hazards for OS based on MAPS data.

a. Please provide a similar figure to CS Figure 28, examining the smoothed hazards for OS based on the SACT data and CheckMate-743 data (separately per data source and separately per treatment) and elaborate on the implications of this figure.

The smooth hazards for OS from CheckMate-743 and the digitized SACT data are presented in Figure 9 and Figure 10. As can be seen in Figure 10, the SACT data appears to have a similar hazard function to that presented for the MAPS data in the CS. In Figure 9, it also appears that a similar shape is developing for the PDC arm. The nivolumab + ipilimumab hazard seems to follow a similar pattern until month 22,

but after that the large amount of censoring makes the graph uninformative beyond this timepoint.

Figure 9. Smooth hazards for overall survival for CheckMate-743

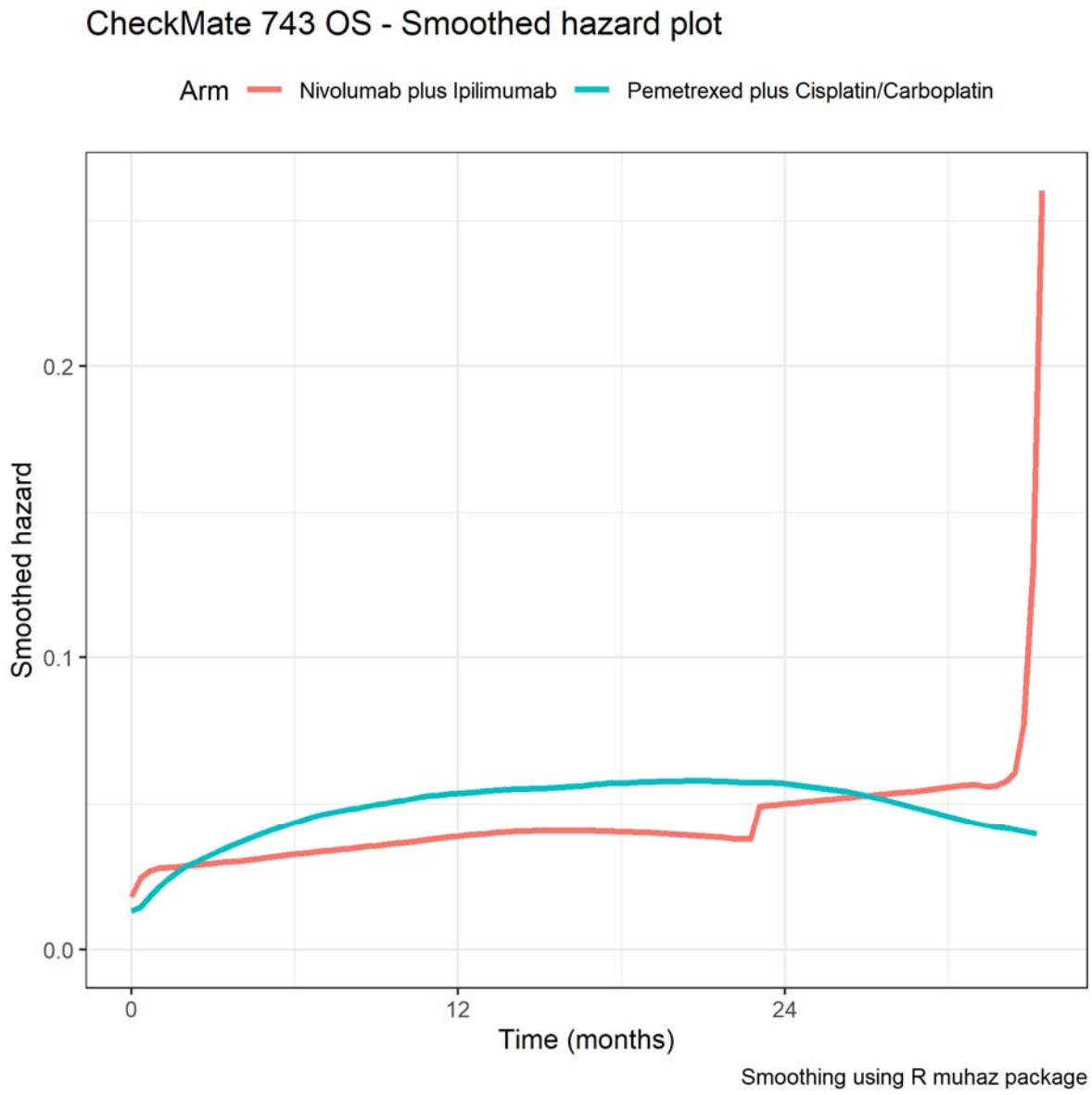
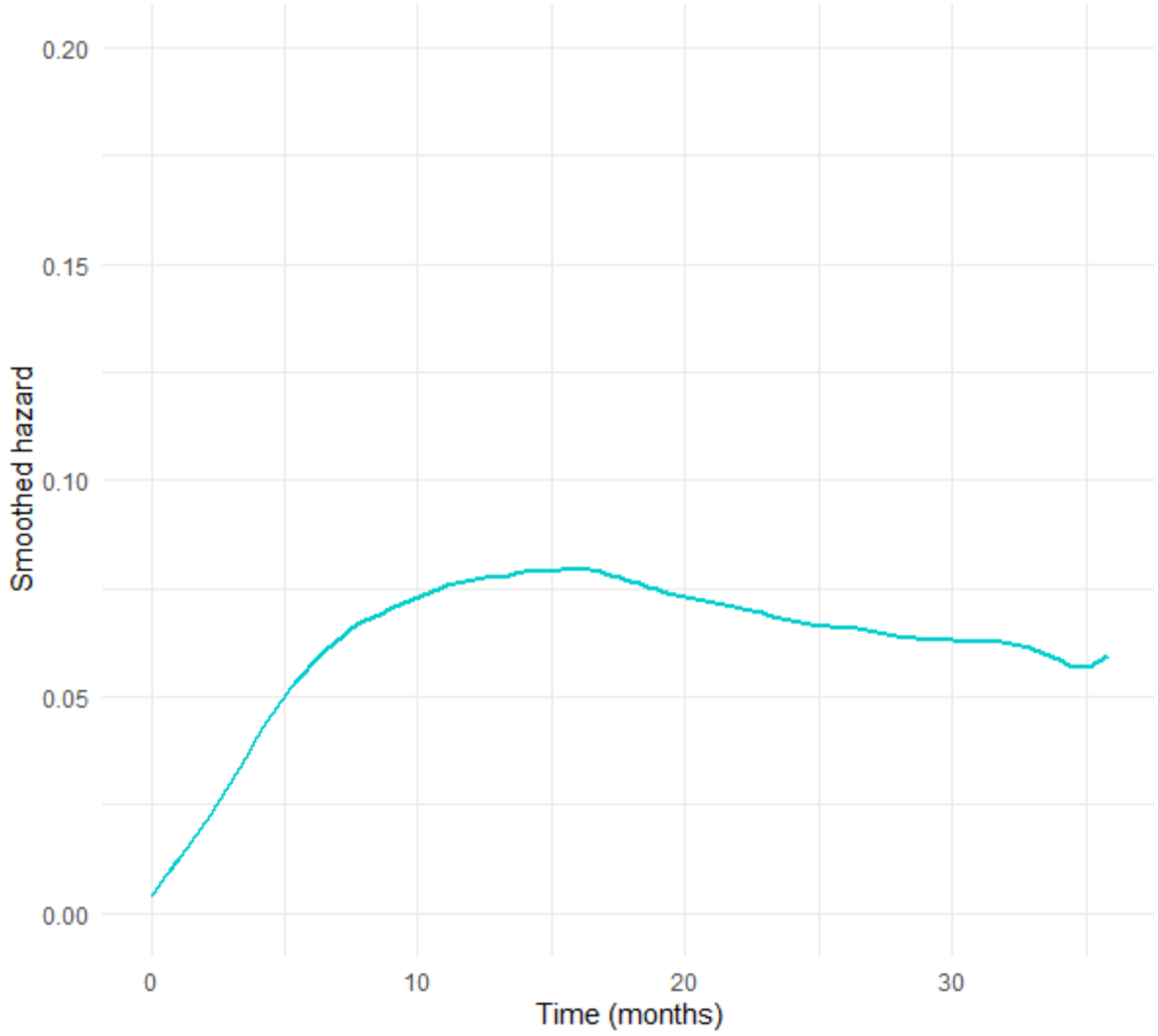


Figure 10. Smooth hazards for overall survival for SACT data



b. Please provide a similar figure to CS Figure 28, examining the smoothed hazards for PFS based on the MAPS data, SACT data and CheckMate-743 data (separately per data source and separately per treatment) and elaborate on the implications of this figure.

We are not aware of any PFS data from SACT. Figure 11 and Figure 12 present the smooth hazards for PFS from the CheckMate-743 trial and the digitized MAPS data, respectively. From visual inspection of the PDC arm of CheckMate-743 and the MAPS trial, the smooth hazards function seems to be broadly aligned with an initial increase in hazards before decreasing almost to a plateau over time.

Figure 11. Smooth hazards for PFS data for CheckMate-743

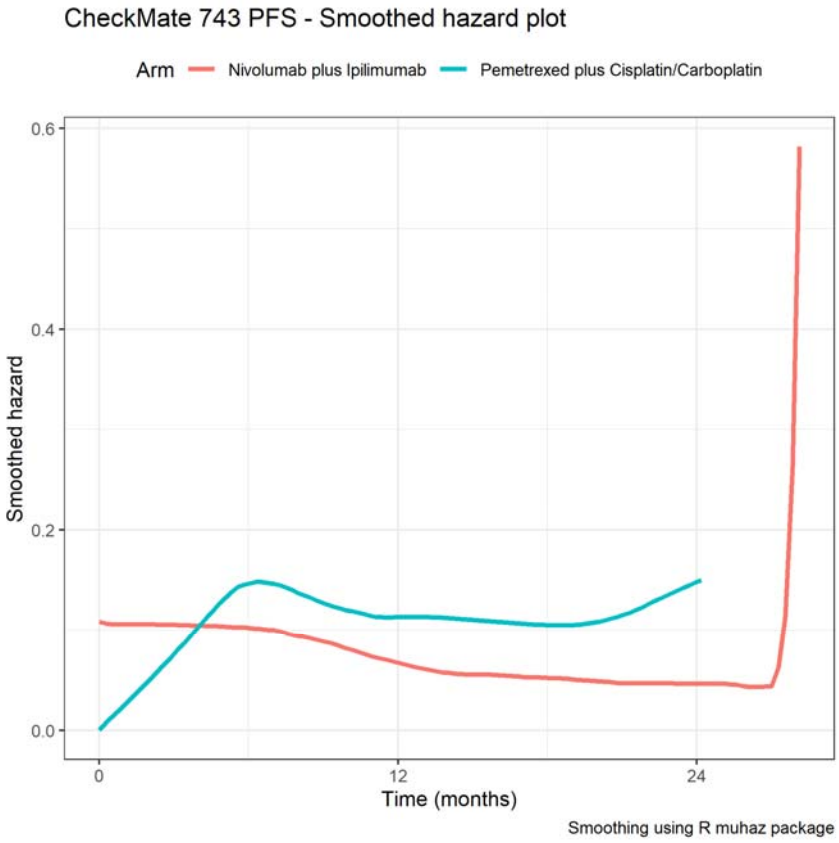
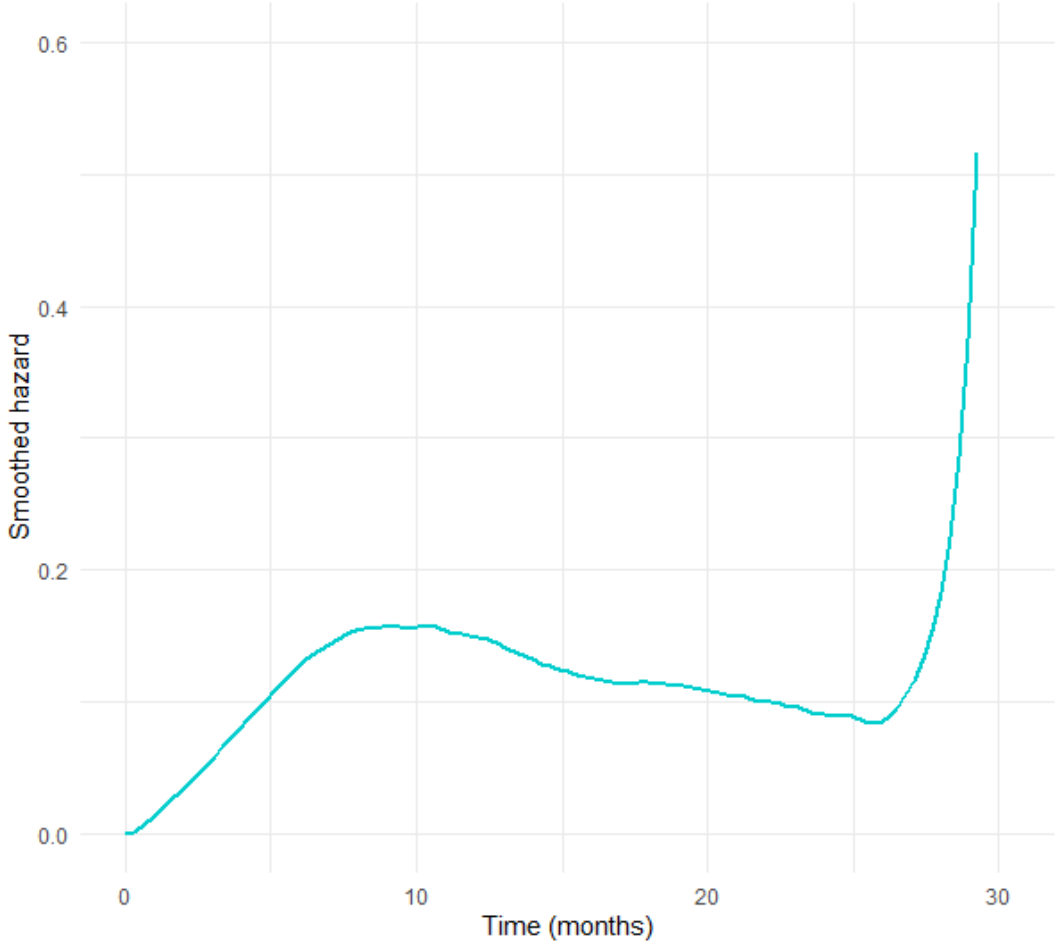


Figure 12. Smooth hazards for PFS for the MAPS PDC arm



Note: for purpose of comparison to the CheckMate-743 data in Figure 11, the y-axis of the figure has been capped at 0.6 where the hazard from MAPS continued to rise for the last 9 months of PFS data

c. For OS, the described hazard function for the selected distribution is identical for both PDC and nivolumab + ipilimumab. In particular, the hazard function of the selected distribution should have an initial increase in hazards followed by long-term decreasing hazards (CS section "Heuristics for selection of survival extrapolation for overall survival based on external validation"). Moreover, NICE DSU TSD 14 on survival analysis notes that using different distributions/approaches for the different treatment options would require "*substantial justification, as different models allow very different shaped distributions*". Please justify, given the above, the use of different distributions/approaches to estimate OS for PDC and nivolumab + ipilimumab.

Different distributions were used for the two treatment arms to ensure that the selections had good statistical and visual fit and were clinically plausible. Given that

nivolumab + ipilimumab has a markedly different mechanism of action compared to PDC, it is also plausible that this would result in differences in the underlying hazard function over time. Immunotherapies have now also shown long-term benefits compared to chemotherapy[24] which further underpins the plausibility of using different distributions for the individual arms to capture the differences in long term hazard functions. We acknowledge that the curve selection might diverge from aspects of our heuristics for the selection of survival extrapolations for overall survival based on external validation. However, the divergence in curve selection was due to distributions selected based on the heuristics for hazard function not resulting in long-term survival predictions deemed most clinically valid; alternative selections of distributions were therefore made for the base case analyses.

B7. According to the CS, the MAPS data can be used to inform PDC OS extrapolations as "*trajectory of the survival curves is relatively aligned after 10 months*". However, based on CS Figure 27, it can be questioned whether the MAPS and PDC (based on CheckMate-743 data) OS curves are similar. The company furthermore consider this selection heuristic: "*Survival predictions* [for the PDC arm] *should result in long-term survival probabilities that continue to be slightly below the observed survival from the MAPS study".*

a. Please justify why the MAPS data can be used as a benchmark to inform PDC OS extrapolations. Please comment on any differences in patient characteristics or treatment strategies between Checkmate-743 and MAPS that may inform the selection heuristic referenced above.

As presented in the CS and in our response to question B5j, there is a paucity of long-term survival data available for patients with MPM. Clinical input was sought, and advisory boards held in preparation for our submission and the MAPS data was reported by the clinical experts consulted as the most clinically relevant to use. Patients characteristics between the MAPS trial and the CheckMate-743 trial are overall broadly aligned. Thus, the MAPS data was considered the most representative and most appropriate external data source to use for validation. However, as the pointed out by the ERG, there are differences between the MAPS OS and the OS from CheckMate-743. There will always be some differences between data collected in two different trials even for the same patient population. In

this case, the PDC arm of MAPS has a consistently higher OS compared to the PDC arm of CheckMate-743 throughout the trial follow-up period. In addition, MAPS excluded patients aged 75 and over, while in CheckMate-743, 26.2% of patients (n = 79) in the PDC arm were aged 75 and over. With respect to treatment strategies, the authors of the MAPS study primary manuscript acknowledged that OS in both arms may have been improved due to rechallenge with pemetrexed + platinum-based therapy.[22] As such, MAPS provides an upper bound on OS and is a conservative selection.

Thus, for our validation of survival extrapolation a continued lower OS for CheckMate-743 compared to MAPS is deemed clinically plausible.

b. Ideally PDC OS extrapolations are compared with external evidence that is representative for England NHS practice. Please justify that the estimated OS based on the MAPS data is representative for England NHS practice.

Please see our responses to B5j and B7a above. Based on the clinical input received from UK experts, the MAPS data was agreed to be the most representative data to use for external validation.

In the CAS registry study of patients with MPM in England, all SACT-treated patients were treated with PDC.[2] However, the amount of follow-up is limited and does not provide input for extrapolations beyond the MAPS data, but does provide a lower boundary for OS. As such, we can reasonably expect the PDC arm from CheckMate-743 to lie in between the MAPS and CAS registry data.

B8. To estimate PFS in the CS base-case, the generalised gamma distribution is used for nivolumab + ipilimumab while the log-logistic curve is used for PDC. As highlighted in the previous clarification question, according to NICE DSU TSD 14 on survival analysis using different distributions/approaches for the different treatment options would require "*substantial justification, as different models allow very different shaped distributions*".

a. For nivolumab + ipilimumab, the Gompertz PFS curve is not used given the long tail (which was regarded too optimistic). However, the selected generalised gamma distribution, has a relatively long tail as well (see CS

Table 34). Please justify the use of the generalised gamma distribution for nivolumab + ipilimumab given its tail.

The choice of distribution for modelling PFS was as outlined in the CS, guided by a combination of statistical fit, visual fit and clinical plausibility. Given that CheckMate-743 is the first trial of nivolumab + ipilimumab in MPM, no long-term follow-up data are currently available to assess whether the generalised gamma distribution is optimistic or not. However, based on the statistical and visual fit to the data, the generalised gamma distribution together with Gompertz was considered to have the best fit to the data. The clinical experts who were consulted also confirmed that the generalised gamma distribution was the most clinically plausible distribution and was therefore selected as the base case distribution.

b. Please provide data/evidence (e.g. based on MAPS or SACT data) as well as expert opinion to validate the long-term PFS extrapolations (e.g. based on CS Tables 34 and 36).

As noted in response to part a of this question, PFS extrapolations were validated by the clinical experts consulted as part of the development of the CS. UK clinical experts highlighted the limited use of PFS as an outcome in MPM, due to the difficulty in radiological assessment in MPM.

From these interviews, the choice of log-logistic distribution for PDC was considered to result in plausible long-term extrapolations. We are not aware of PFS data being available from SACT data, but have digitised the PFS curves for the MAPS trial.[22] The estimated PFS from the MAPS trial has been added to Table 19 below, together with the alternative distributions fitted to the PDC arm of CheckMate-743. As can be seen in the table, the PFS from MAPS and CheckMate-743 are well aligned. Furthermore, the selected log-logistic distribution is also well aligned with the MAPS data at years 1 and 2, but slightly overestimates the PFS in years 3 and 5. Other distributions that are more closely aligned with the 3- and 5-year PFS from MAPS overestimate the early PFS. Thus, the selected log-logistic distribution is thought to be the best selection also when considering the external evidence from the MAPS trial. Similar to the previous question, as longer-term data is not available for nivolumab + ipilimumab, a validation table is only presented for PDC.

Table 19. Landmark absolute progression-free survival analysis for independent parametric distributions fitted to pemetrexed + cisplatin or carboplatin

		Absolute survival (%)			
Data Set	**Curve**	**Yr 1**	**Yr 2**	**Yr 3**	**Yr 5**
CheckMate-743	Kaplan-Meier	23.8	7.2	0.0	-
MAPS (2016)	Kaplan-Meier	21.1	6.5	0.9	0.3
Pemetrexed + cisplatin or carboplatin extrapolation	Log-logistic	25.6	6.7	2.8	0.9
	Generalised gamma	28.4	5.8	1.4	0.1
	Gamma	29.4	4.5	0.6	0.0
	Log-normal	28.4	8.0	2.9	0.6
	Weibull	31.1	4.5	0.4	0.0
	Gompertz	32.9	6.5	0.6	0.0
	Exponential	31.8	10.1	3.2	0.3

Mos = months; Yr = year.

c. Please justify, given the above, the use of different distributions/approaches to estimate PFS for PDC and nivolumab + ipilimumab.

As detailed in responses to part a and part b, different distributions were used for the two treatment arms to ensure the selections had good statistical and visual fit and were clinically plausible. When clinical experts were consulted during the development of the submission, survival predictions based on the same distribution for both arms were not considered to provide the most plausible long-term survival. This inability to model both arms with the same distributions is also justified given the different mechanism of action that nivolumab + ipilimumab has compared to PDC (please also see our response to B6c). Given this difference it is also plausible that this would result in differences in the underlying hazard function over time.

B9. CS Figure 27 indicates that the SACT OS is (substantially) below the OS estimated for the CheckMate-743 PDC arm. Please elaborate on the implications for the generalisability of the OS estimated for the CheckMate-743 PDC arm to England NHS practice.

We acknowledge that the trial population may have slightly different demographic characteristics than the population expected to receive treatment in the UK setting. However, we do not anticipate that this would have a significant impact on clinical outcomes and that the CheckMate-743 trial provides the best available evidence for nivolumab + ipilimumab in this indication.

Clinical opinion from two UK experts sought during model development confirmed that there were few differences between the CheckMate-743 trial population and the population that would be treated in UK clinical practice, and the trial population was representative. The experts agreed that the survival rates in the control arm of CheckMate-743 were slightly higher than observed in real-life and observed in some previous clinical trials. Experts stated that this may be due to higher rates of subsequent treatment in CM-743 than real-life practice; however, survival since the original licensed therapy may also have improved in recent years with current second-line treatments.

In general, patients recruited to clinical trials are usually fitter with fewer comorbidities and a more homogeneous population when compared with real-life clinical practice, which can impact outcomes. As treatment with PDC has a limited survival benefit in MPM, fit patients are routed into trials as a priority, while a 'watch and wait' approach can also be used in the NHS for patients with low volume, epithelioid disease. Therefore, in clinical practice, less fit patients receive PDC on the NHS, including ECOG PS2 patients (as fitter PS 2 patients will be considered for 1L PDC in the NHS, sometimes with the assistance of steroids) which could partly explain the lower OS.

B10. In the CS base-case no treatment waning was assumed, i.e. the PFS and OS were assumed to be different for PDC and nivolumab + ipilimumab for the whole duration of the time horizon.

a. Please justify the assumption of no treatment waning, i.e. that there is a lifetime difference in PFS and OS based on the initial treatment.

As pointed out in the CS, there is long-term evidence of a robust and durable treatment effect lasting beyond discontinuation for immunotherapies.[24] Thus, a continued treatment effect has been assumed over the lifetime horizon of the model.

b. Please provide an updated economic model and scenario analyses assuming treatment waning (at different time points).

The model has been updated so that the effect of treatment waning can be investigated. The model has been set up so that a time point from which the treatment effect would start to deteriorate can be selected and a timepoint at which a

treatment effect would no longer be incurred (Settings sheet E48:F52). A scenario analysis where the treatment effect is assumed to start deteriorating at year 5 and then decrease linearly to no treatment effect at year 10 is presented in the Table 20 below.

Table 20. Revised base-case incremental results of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin

Technologies	Total costs (£)	Total LYGs	Total QALYs	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per QALY, £
Nivolumab + ipilimumab	xxxxxx	xxxxxx	xxxxxx				
PDC	xxxxxx	xxxxxx	xxxxxx	53,362	0.641	0.513	104,000

Inc = Incremental; LYG = life-year gained; QALY = quality-adjusted life-year.

Adverse events

B11. In Table 39 of the CS, proportions of adverse events are presented.

a. Please provide the source for, as well as calculations of the adverse event rates presented in Table 39.

The incidence of ≥ grade 3 drug-related adverse events were taken from Table 8.5-2 in the CheckMate-743 CSR. This table includes events occurring in ≥ 5% of all patients. Data in CSR supplementary table S.6.2.2 were also used to include ≥ grade 3 events occurring in ≥ 2% of all patients.

Please note that fatigue was mistakenly included in Table 39; this event occurs in less than 2% of patients and was not included in the model. In addition, colitis should have been included because ≥ grade 3 colitis was experienced by 2.3% of patients in the nivolumab + ipilimumab arm and 0.4% of patients in the PDC arm. Colitis has been included in the model for the revised base case. Parameters for the cost of managing colitis and the disutility associated with colitis were assumed to equal the values for diarrhoea, which is a main symptom of colitis.

b. Please provide justification for using only ≥ grade 3 adverse events. Please also provide justification for excluding adverse events with an incidence < 2%.

Only ≥ grade 3 adverse events were included, because it was not expected that minor adverse events (grade 1-2) would have any significant impact on costs or disutility.

A 2% cut-off was chosen to capture all adverse events that would have a meaningful impact on costs and disutility.

c. Please include all-causality (treatment-emergent) adverse events instead of only treatment-related adverse events, change the restriction on the incidence to 1% (in line with A14) and provide a new Table 39 with these changes. Please also incorporate these adverse event rates as a scenario on the model.

Rates of grade 3 or 4 all-cause adverse events occurring in at least 1% of patients from CheckMate-743[12] are presented in Table 11, in response to question A15.

Including adverse events in the model based on these criteria would require the addition of 23 additional adverse events. Due to the very low incidence of these events and small differences between treatment arms, the impact to the ICER would be minor. Moreover, relevant cost and disutility data are not available for many of these adverse events. On this basis, the 23 additional adverse events have not been included in the model.

Health state utility values

Additional Explanation of Original Analysis

We would firstly like to provide additional information relating to the utility information presented in the original submission document, which was based on the Utility Analysis Report and additional supplementary appendices.[25]

Health-related quality of life data were planned to be collected in CheckMate-743 using the EQ-5D-3L questionnaire for all randomised patients both on-treatment and off-treatment (follow-up and survival follow-up visits); as per protocol design patients on Arm A (nivo+ipi) were treated until disease progression, unacceptable toxicity, or a maximum treatment duration of 2 years; patients on Arm B (chemo) were treated for 6-cycles or until disease progression or unacceptable toxicity. In Arm A, treatment

beyond progression was permitted if the subject had investigator-assessed clinical benefit and was tolerating treatment.

As per study protocol, EQ5D data were collected for all randomised patients during the on-treatment phase pre-progression. Patients entered the follow-up phase after discontinuation of treatment; EQ5D data were also collected during the follow-up (off treatment) phase (until death or end of study).

The date of progression as per BICR progression date was used in the utility analysis to determine pre/post progression status.

EQ-5D Data Availability

582/605 (96.2%) of all randomised patients had at least one EQ5D utility value Table 21). All available EQ5D utility data was used in analysis; a total of 4,899 EQ5D utility values were included in analysis.

Table 21. EQ-5D Data Availability

	Overall		**Nivo+Ipi**		**Chemo**	
	N patients	N Obs	N patients	N Obs	N patients	N Obs
All Randomised	605		303		302	
EQ-5D Utility Value	582	4899	298	2885	284	2014

Source: Bristol-Myers Squibb[25]: Table 1.1 and Table 14.9.1

Missing Data

There are 23 subjects with completely missing EQ5D utility data (3.8% of all randomised).

At the time of the original analysis, the demographic characteristics of the PRO Analysis population were compared with the all randomised population and it was concluded that the PRO Analysis population was representative of the all randomised population. The completion rate at each visit on-treatment (on-treatment weeks until Week 120 post randomisation) and at survival follow up visits was reviewed (in the EQ5D PRO Analysis population). The completion rates out of expected (defined as those alive, on-treatment and not withdrawn from study) is

above 80% at all on-treatment visits (exception week 8 and week 108 at 78%); and was similar in both treatment arms. At follow-up, the expected number of subjects for utility analysis at FU1 was n=292, based on information on the number of patients at the first follow-up visit with EQ5D utility data available; by study design this is much lower than all randomised patients due to patient deaths and withdrawal from the study.

A detailed consideration of all the other missing data for the on-treatment period was conducted at the time of the original analysis. The patterns of missing data grouped by the last on-treatment timepoint by treatment arm were reviewed and presented in Bristol-Myers Squibb[25] (Appendix A: Missing data patterns (Source: Tables 3.1.2 & 3.2.2).) The last possible assessment was defined for these tables for Arm A as Week 120, and for Arm B as Week 72 based on the data collected. The missing data definitions were defined as “monotone” missing (data present for all assessments up to a point and then dropped out; this may be due to progression, death, etc.; e.g., XXXXXXX000000000000), “intermittent” missing (non-missing data at last assessment, but one or more missing assessments; e.g., XXXXXXXXOXXXOXXXXX) or “mixed” missing (last-assessment and others are missing; e.g., XXXXXXXXOXXXOXOOOO). In Arm A (Nivo + Ipi), 149 subjects (49.2%) had monotone missing – which suggests that they had complete assessments up to a certain timepoint (which may be treatment discontinuation, death). 146 subjects (48.2%) had “mixed” missing patterns, which indicates potentially relevant missing data as it clearly was expected. In Arm B (chemo), 186 subjects (61.6%) had monotone missing and 96 subjects (31.8%) had “mixed” missing patterns. The detailed missing data patterns indicate the types of patterns observed, and for both treatment arm there is a variety of patterns/timings of the mixed missing data with generally only one, or a low number of subjects with any single pattern of mixed missing data (i.e., the intermittent missing data pattern in this case).

At the time of the original analysis, the review of these patterns of missing data indicated that during the on-treatment period an assumption of data being missing at random could be considered appropriate. At the time of the original analysis, the

patterns of missing data in the off-treatment period were not reviewed in detail as fewer patients were expected to have off-treatment data.

Calculation of Utility estimates

At the time of the original analysis, to estimate utility values for health states of interest, a number of mixed models (MMRM, mixed model repeated measures) were fitted to the data, using SAS PROC MIXED, to account for repeated EQ5D assessments per subject within a health state. A repeated mixed model approach is generally regarded as suitable for estimations in the presence of MAR (missing at random) missing data. The health states of interest were defined as pre-progression and post-progression, using the date of progression as defined by BICR. EQ5D assessments were considered pre-progression until date of progression. Models including and excluding treatment were considered. The MMRM model without treatment included health state (2 states: pre-progression and post-progression) as a fixed effect, and a random intercept for each subject to account for repeated measurements within each subject. A MMRM model with treatment included health state (2 states: pre-progression and post-progression), treatment and treatment*health state interaction as a fixed effect, and a random intercept for each subject to account for repeated measurements within each subject. Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics based on maximum likelihood estimation were used to examine the extent of improvement in model fit after including treatment.

The LS mean utility values presented in the original submission for overall (pre and post progression health states) were obtained from a MMRM model without treatment; the LS mean utility values for each treatment arm (pre and post progression) were obtained from a MMRM model with treatment included.

The number of subjects, number of observations, and LS mean utility values in each state in the models are provided in Table 22. The model fit statistics suggested that the model including treatment was a better fit to the data.

Table 22. LS mean utilities by health state

	Overall			Nivo+Ipi			Chemo		
Health State	**N patients**	**N Obs**	**LS mean (SE)**	**N patients**	**N Obs**		**N patients**	**N Obs**	
Overall	582	4899	0.677 (0.008)	298	2885		284	2014	
Pre-Progression	580	3733	**0.734** (0.008)	297	2196	**0.737** (0.012)	283	1537	**0.733** (0.012)
Post-progression	373	1166	**0.620** (0.010)	190	689	**0.652** (0.014)	183	477	**0.580** (0.015)

Source: Bristol-Myers Squibb[25] (Tables 14.19.1, 14.19.2, and 14.19.3)

B12. Priority question. Health state utility values are, according to CS Figure 43 key drivers of the cost-effectiveness results.

a. CS Table 37 presents the EQ-5D-3L assessment schedule. Please provide, per measurement timepoint, separately for Nivolumab + Ipilimumab and Pemetrexed + cisplatin/carboplatin:

    a. the total number of EQ-5D-3L responses

    b. estimated mean utility values and standard error

    c. a breakdown how many patients were progression-free and had progressed disease

    d. a breakdown how many patients were on and off treatment (i.e. receiving Nivolumab + Ipilimumab or Pemetrexed + cisplatin/carboplatin)

The number of patients expected and observed and the mean utility value, by progression/progressed health state by treatment arm and for all on-treatment and off-treatment visits are presented in Bristol-Myers Squibb[25] (Appendix B: Completion rates by treatment and progression status (Source: Tables 19.1 & 19.2)).

On-treatment, in both arms, the mean utility score is higher in the pre-progression state than post progression. In the nivo+ipi arm, the mean utility value increases over time; in the chemo arm there is a similar trend until Week 18. In the Chemo arm on-treatment the number of subjects with data is low after Week 18 (as expected with 6 cycles of chemo treatment). Also, there are some patients in the chemo arm with on-

treatment data post-progression which is slightly unexpected – although this is noted to be fewer than 10 patients (<3% of those randomised).

Off-treatment, in the nivo+ipi arm, more patients are post-progression than pre-progression. In the chemo arm at the initial follow-up visit (FU1) more patients are progression free than progressed, although at later timepoints the majority of the off-treatment patients are post-progression.

e. the extent of missing data observed

There are 23 patients with completely missing EQ-5D data (3.8% of all randomised); 5 in the nivo+Ipi arm and 18 in the chemo arm.

The extent of missing data by visit can be seen in Bristol-Myers Squibb[25] Appendix B: Completion rates by treatment and progression status (Source: Tables 19.1 & 19.2). The completion rate at each visit on-treatment (on-treatment weeks until Week 120 post-randomisation) and at survival follow-up visits is presented showing data available and expected. Overall, the completion rates out of expected (defined as those alive and not withdrawn from study) is above 80% at all on-treatment visits and was similar in both treatment arms. At follow-up, the expected number of subjects for utility analysis at FU1 was n=292, based on information on the number of patients at the first follow-up visit with EQ-5D utility data available; by study design this is much lower than all randomised patients due to patient deaths and withdrawal from the study.

During the on-treatment phase there are timepoints when data were expected but not observed – this ranged from 1 up to 58 patients with missing data at any one timepoint – and is similar in both treatment arms (note this includes those completely missing any PRO assessment). In the follow-up phase the number of available and expected observations was much lower than on-treatment; the calculation of expected was assessed based on number of patients alive and on-study.

For further information about detailed patterns of missing data in the on-treatment phase please refer to the information included in the introductory section and Appendix A: Missing data patterns (Source: Tables 3.1.2 & 3.2.2) of Bristol-Myers Squibb[25]. This detailed assessment of patterns of missing data, lead to the

assumption that the missing data at each visit could reasonably be considered to be missing at random (MAR).

b. Please explain, with appropriate justifications, how the utilities reported in Table 38 were estimated. Specifically, what regression model was used, and whether within-subject correlation is accounted for. If within-subject correlation is not accounted for then please rerun the analyses taking within-subject correlation into account.

To estimate utility values for health states of interest (pre-progression and post-progression), a number of mixed models (MMRM, mixed model repeated measures) were fitted to the data, using SAS PROC MIXED, to account for repeated EQ5D assessments per subject within a health state (i.e., accounting for within-subject correlation). The health states of interest were defined as pre-progression and post-progression, using the date of progression as defined by BICR. EQ5D assessments were considered pre-progression until date of progression. Models including and excluding treatment arm were considered. The MMRM model without treatment arm included health state (2 states: pre-progression and post-progression) as a fixed effect, and a random intercept for each subject to account for repeated measurements within each subject. A MMRM model with treatment arm included health state (2 states, pre-progression and post-progression), treatment-arm and treatment-arm by health state interaction as a fixed effect, and a random intercept for each subject to account for repeated measurements within each subject. An unstructured covariance matrix was used. Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics based on maximum likelihood estimation were used to examine the extent of improvement in model fit after including treatment.

The LS mean utility values presented in the original submission for overall (pre- and post-progression health states) were obtained from a MMRM model without treatment arm; the LS mean utility values for each treatment arm (pre- and post-progression) were obtained from a MMRM model with treatment arm included.

c. Please explain, with appropriate justifications, how missing data were handled and the implications of this approach.

At the time of the original analysis, the competition rate, patterns of missing data and considerations of reasons for missing data were reviewed. As noted previously, there were 23 subjects with completely missing EQ5D data (3.8% of all randomised). Therefore, this is the key proportion of missing data when considering health state analysis (as all other subjects contributed data to at least one health state). A summary of the demographic and baseline clinical characteristics of the subjects with EQ5D data indicated that the subjects with available EQ5D data were consistent with the characteristics of the all randomised population.

A detailed review of missing data identifies that there were subjects with intermittent missing data patterns in both treatment arms, with up to a maximum of 20% of data missing at any single timepoint. Considering all timepoints (and including the completely missing patient data), the EQ5D utility data was found to be 89% complete (4,899 EQ5D assessments, out of an expected 5,488). The patterns of missing data did not indicate strong patterns in the data missing by visits, and therefore a general assumption of data being missing at random was assumed.

A repeated mixed model approach is generally regarded as suitable for estimations in the presence of MAR (missing at random) missing data, as well as other missing data.

Therefore, in the original analysis, all available EQ5D data were used, utility scores for health states were estimated from a MMRM to account for within-subject repeated measures within health states and provide robust estimates in the presence of low levels of missing data (<5% missing) within health states.

d. Please compare patient characteristics of patients which were included and patients excluded from utility values calculations for both treatment groups separately and for the whole trial population combined (independent of treatment groups).

There were 23 patients (3.8% of all randomised) with completely missing data; 5 in the nivo+ipi treatment arm and 18 in the chemo arm. Baseline demographic and disease characteristics for all 23 patients and for each treatment arm are provided in full in Bristol-Myers Squibb[25] Appendix C: Demographics by inclusion & exclusion

(Source: Tables 20.1-20.3). The patients had similar baseline demographic and disease characteristics to the patients with EQ5D data available.

e. Please clarify what the likely causes of missing data were and what the potential impact of these missing data on the estimation of the utility scores would be, separately for patients who had completely and partially missing utility data.

The 23 patients (3.8%) with completely missing data had similar baseline demographic and disease characteristics to those patients with EQ5D assessments, and no other known reasons to be completely missing, although it is noted that there were more patients with completely missing data in the chemo arm compared to the nivo+ipi arm. As the proportion of subjects with completely missing data was low, it was considered that these subjects would be unlikely to influence the estimated utility values greatly.

As per the study design, in the absence of progression (or toxicity), patients remained on treatment for up to 2 years (nivo+ipi) or 6 cycles of chemotherapy (approximately 18 weeks). Patients then entered the follow-up phase. EQ5D data should have been collected both prior to progression and post progression; therefore, just disease progression status should not influence expected data. The amount of available data in the off-treatment phase is lower than on-treatment phase – however, it is possible that subjects died whilst on-treatment and that therefore data is not expected. The schedule of assessments in the follow-up phase (every 12 weeks) was much longer than the on-treatment phase and therefore this may have contributed to less data available in the post-treatment phase.

When considering the data within health states, there were a large number of subjects and assessments within the health states, despite some intermittent missing data, and therefore as the within-subject correlation was taken into account in the model, it is felt that the presence of the intermittent missing data was unlikely to influence the estimated utility values greatly.

f. Please recalculate the utility estimates reported in CS Table 38 while imputing missing values (for the patients with completely missing utility data and patients with partially missing utility data) using multiple imputation

(incorporating potential explanatory variables and using at least 10 imputations).

a. Please provide in detail, the methods used to impute and pool the utility data

In the limited timeframe of this request, a multiple imputation method using SAS PROC MI and PROC MIANALYSE was implemented, which creates multiple imputed datasets based on the original data available, enables calculation of mean utility value, and allows valid statistical inferences to be generated by combining results from the analyses.

For 2-state (progression free versus progressed), the MI was carried out as follows. Firstly, the mean of EQ-5D utility index scores by progression status was calculated for each subject. Secondly, the MI was carried out separately by treatment arm, with 10 datasets imputed by using SAS PROC MI with variable of logarithmic transformed survival time (days from date of randomization to last known alive date or death date), demographic and clinical variables at baseline and 2 variables for means by progression status (i.e., health state of interest). The seed (64587866) was provided to reproduce results. Numbers of burn-in and thinning were 10000 although the EM algorithm adopted by PROC MI converges around 145 iterations. After imputation, any values greater than 1 were truncated to 1 and any values less than -0.594 were set to -0.594. Thirdly, mean and standard error of each of 2 health states were calculated by imputed datasets by treatment arm. Fourthly, multiple imputed means were combined to get the utility estimates for each state by arm by using SAS PROC MIANALYZE.

The baseline demographic and clinical variables included were: age, gender, region, ECOG PS, smoking status, histology status, PD-L1 status, prior radiotherapy, and stage of disease.

MI for 4-state (progression free & on-treatment, progression free & off-treatment, progressed & on-treatment, progressed & off-treatment) was carried out similarly, using 4 health states and firstly calculating the mean of EQ-5D utility index scores by progression status and on/off treatment for each subject.

b. Please elaborate on the plausibility of the imputed utility values

A limitation of this imputation approach is that whilst it is possible all subjects would be in pre-progression and post-progression health state, the observed data illustrate that this was not the case (e.g., patients die and do not enter post-progression). Therefore, it is not necessarily appropriate to consider the data for all health states (such as post-progression) to be "missing" for all subjects. Also, in the observed data, subjects have very different numbers of repeated assessments in the health states, and this complexity is not clearly adjusted for in the imputation method applied due to the focus on the imputation at the health state level.

The utility estimates using PROC MI and PROC MIANALYSE to impute data are provided in Table 23.

Table 23. Utility estimates based on 2-state imputation model using PROC MI and PROC MIANALYSE methodology

	A: Nivo+Ipi		**B: Chemo**	
Progression status	LS mean	SE	LS mean	SE
Progression free	0.718	0.013	0.720	0.013
Progressed	0.611	0.019	0.515	0.026

Source: Bristol-Myers Squibb[25]Table 22.1.3

The estimates from this 2-state imputation model are lower than the PROC MIXED LS mean estimates used in the original model and show more differences between treatments. It does not seem likely to be an improved estimate of utilities for each health state due to potential biases mentioned above, in particular accounting for within-subject correlation adequately. Also given that the level of missing data is low (3.8% completely missing), it seems possibly unrealistic that estimates should be impacted to such an extent if the imputation applied was robust in this situation.

c. Please provide an updated economic model as well as scenario analysis incorporating these newly calculated utility values

We have provided an option in the economic model to select the utility values based on the 2-state imputation model (Utility sheet E8:H13). However, we propose that utilizing the imputed estimates for the utilities may lead to a biased estimate of utilities as discussed in response to part (b) above.

Table 24. Scenario results of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin in first-line unresectable MPM with 2-state imputed utility values

Technologies	Total costs (£)	Total LYGs	Total QALYs	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per QALY, £
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
PDC	[redacted]	[redacted]	[redacted]	54,417	0.916	0.690	78,891

Inc = Incremental; LYG = life-year gained; QALY = quality-adjusted life-year.

g. Please provide the Table requested above (CS Table 38 while imputing missing values) stratified for patients being on treatment (i.e. receiving Nivolumab + Ipilimumab or Pemetrexed + cisplatin/carboplatin) or not.

This is provided in Table 25. As discussed in response to Question B12 (f) part (b) above, the 4-state model with imputations has potentially even more caveats, especially as it is not expected by study design that subjects would enter all 4 health states, and therefore the available data within the 4 health states are limited.

The methodology for imputation is using PROC MI and PROC MIANALYSE, as described above, including 4 health states.

Table 25. Utility estimates based on 4-state imputation model

Progression status	On/Off Treatment	A: Nivo+Ipi		B: Chemo	
		mean	SE	mean	SE
Progression free	On	0.719	0.013	0.721	0.013
	Off	0.683	0.017	0.666	0.023
Progressed	On	0.656	0.021	0.643	0.019
	Off	0.558	0.027	0.475	0.028

Source: Bristol-Myers Squibb[25] Table 22.2.3

h. Please rerun the analyses performed to obtain the utility values presented in CS Table 38 (i.e. original approach from the CS) stratified for patients being on treatment (i.e. receiving Nivolumab + Ipilimumab or Pemetrexed + cisplatin/carboplatin) or not.

The estimated LS mean utilities from a 4-state model (on/off treatment & pre/post progression) are presented from a MMRM modelling approach including

treatment_arm, on/off treatment & pre/post progression (4 level health states) and treatment_arm by health state interactions as fixed effects and a random intercept for subject to account for within-subject correlation.

For information, the number of subjects and observations in each health state are provided in Table 26.

Table 26. Number of subjects and observations in each health state

Progression status	On/Off Treatment	A: Nivo+Ipi		B: Chemo	
		#Subs	#Obs	#Subs	#Obs
Progression free	On	297	2053	283	1260
	Off	50	143	135	277
Progressed	On	126	319	39	54
	Off	147	370	171	423

Source: Bristol-Myers Squibb[25] Table 21.1.1

The LS mean utility estimates from a 4-state MMRM model are provided in Table 27.

Table 27. LS mean utility estimates from a 4-state MMRM model

Progression status	On/Off Treatment	A: Nivo+Ipi		B: Chemo	
		LS mean	SE	LS mean	SE
Progression free	On	**0.736**	0.012	**0.734**	0.012
	Off	**0.733**	0.021	**0.719**	0.017
Progressed	On	**0.708**	0.016	**0.638**	0.030
	Off	**0.607**	0.015	**0.572**	0.015

Source: Bristol-Myers Squibb[25] Table 21.1.2

The model fit criteria are included in Bristol-Myers Squibb[25] Appendix D: LS Mean Estimates for Health States (Source: Tables 21.1.1-21.1.3); statistically the 4-state model is a better fit to the available data than a 2-state (pre/post progression) model.

i. Please provide an updated economic model as well as scenario analysis incorporating the estimated utility values in response to sub-questions g and h (i.e. utility values estimated stratified for patients being on treatment or not with and without imputation).

As discussed in response to 12b and c we propose that utilizing the imputed estimates for the utilities may lead to a biased estimate but have included it into the model for completeness. Fully including the updated 4-state utility analyses into the economic model would require substantial restructuring of the model as time on treatment is currently not split between progression free and progressed disease. Thus, it has not been feasible for the updated utility analyses to be incorporated into the economic model as requested. However, to partially meet the ERG's request, the model has been updated with the progression-free health state has been split into on or off treatment. This requires the assumption that all patients on treatment are progression free. Given that treatment could be continued based on the clinician's decision this is not fully reflective of the trial, or how it would be anticipated to be in clinical practice. However, the majority of patients on treatment are in the progression-free health state and thus the assumption would allow for investigation of the potential impact of including utilities adjusted for being on or off treatment. As can be seen from the table below the inclusion of utility values differentiated by treatment status do however have a very small impact on the overall results.

Table 28. Scenario results of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin in first-line unresectable MPM with 3-state imputed utility values

Technologies	Total costs (£)	Total LYGs	Total QALYs	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per QALY, £
Nivolumab + ipilimumab	xxxxxx	xxxxxx	xxxxxx				
PDC	xxxxxx	xxxxxx	xxxxxx	54,417	0.916	0.697	78,065

Inc = Incremental; LYG = life-year gained; QALY = quality-adjusted life-year.

Table 29. Scenario results of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin in first-line unresectable MPM with 3-state utility values

Technologies	Total costs (£)	Total LYGs	Total QALYs	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per QALY, £
Nivolumab + ipilimumab	xxxxxx	xxxxxx	xxxxxx				
PDC	xxxxxx	xxxxxx	xxxxxx	54,417	0.916	0.706	77,036

Inc = Incremental; LYG = life-year gained; QALY = quality-adjusted life-year.

Resource use and costs

B13. Priority question. The mean number of doses reported in CheckMate-743 applied in the first model cycle were used to calculate treatment costs in the company's base-case (approach 1). Kaplan-Meier estimates for time to treatment discontinuation were used in a scenario (approach 2). No parametric survival analysis was performed because *"the parametric curves could not accurately reflect the treatment stopping rule for nivolumab + ipilimumab and do not reflect the treatment discontinuation that is displayed by the KM curve for pemetrexed + cisplatin or carboplatin"*. The ERG considers that approach 1 may be biased because the mean number of doses do not take right censoring into account (see Wijeysundera et al https://doi.org/10.2147/ceor.s31552). Approach 2 does not include uncertainty in the PSA. According to appendix N, the health economic experts agreed that *"that the CM-743 time-to-treatment discontinuation K-M curves were the best available evidence to inform treatment duration".* The ERG agrees with the experts, but also considers that parametric survival analysis on this evidence may potentially be preferred, and that it should be explored in a scenario.

a. Please enable a scenario in the model file in which parametric survival analysis for time to treatment discontinuation (TTD) is used. Differential distributions could be used (e.g. the best-fitting generalised gamma for the nivolumab + ipilimumab arm and Gompertz for the pemetrexed + cisplatin arm as reported in Appendix K). The stopping rule for nivolumab + ipilimumab can be included by discontinuing all patients still on treatment at 24 months. Missed and delayed doses can be reflected for both arms using dose intensity as informed by Checkmate-743. No stopping rule will then be required for the pemetrexed + cisplatin arm.

As outlined in the CS (Document B, page 100), the mean number of doses from the trial was considered by UK clinical experts as the most appropriate for estimating the treatment costs. The rationale for this, as stated in the CS, is because the KM data (or parametric distributions if those provide good fit) does not adequately capture delayed or missed doses. The input received from the health economic experts (cited above) related to comparisons between the KM data and the poorly fitting

parametric curves. Thus, there was not an argument for KM being a better alternative to the mean number of doses.

We acknowledge that the mean number of doses does not account for right censoring as pointed out by the ERG, however, given that the minimum follow-up time is 22.1 months, the median is 29.7 months and the stopping rule for treatment is at 24 months, the duration of therapy data is mature. Thus, right censoring would be anticipated to have a minimal impact on the final estimates of doses received and we maintain that the mean number of doses is the most appropriate approach for estimating the treatment costs.

However, to allow for the alternative assumptions of duration of therapy to be fully explored, updated duration of therapy data per treatment in the nivolumab + ipilimumab regimen has been requested within BMS. This will ensure that delayed or missed doses for each treatment within the regimens can be captured as adequately as possible in the analyses. BMS will follow up with updates to the model with KM and parametric analyses once availability of data has been confirmed and the data analysed.

b. Please provide a comparison of TTD as observed in the pemetrexed + cisplatin/carboplatin arm in Checkmate-743 with MAPS and SACT data for validation purposes.

Figure 13 presents the time to treatment discontinuation data for pemetrexed + cisplatin/carboplatin arm in Checkmate-743 and SACT. We are unaware of similar data being available for the MAPS trial and have thus not been able to create a figure with all 3 data set as requested.

Figure 13. CheckMate-743 and SACT; Kaplan-Meier plot of time to treatment discontinuation

Sources: Baas[26]; Baas[4]

B14. Priority question. Patients in the comparator arm are treated with pemetrexed in combination with either cisplatin or carboplatin. It appears as though costs for both cisplatin and carboplatin are added in the comparator cost calculations (initial treatment), rather than assigning proportions to each. It is currently unclear to what proportions cisplatin and carboplatin are used in the model.

a. Please provide an explanation for how costs for cisplatin and carboplatin (initial treatment) are applied in the model. If necessary, please correct the model to reflect that either cisplatin or carboplatin are used per patient, for example by weighting their costs by their proportion of use (See A13).

The use of cisplatin or carboplatin in combination with pemetrexed is weighted in the model. In the pemetrexed combination, 33% of patients receive cisplatin and 67% receive carboplatin. These input parameters are in cells L29:L30 on the Tx_related_Costs sheet of the model.

Please note that these parameters should have been 34% for cisplatin and 66% for carboplatin. The values are based on data from CheckMate-743 in which 34% of

patients in the chemotherapy group were given cisplatin.[6] These values have been corrected in the model for the revised base case.

b. Please provide information on the generalisability of cisplatin versus carboplatin use to the England NHS context, for example by comparing the proportions used in the model to MAPS or SACT data.

The choice of cisplatin or carboplatin in CheckMate-743 was according to investigator choice, in line with clinical practice in the UK, where both cisplatin and carboplatin is used (see response to question A4).

Data from the EU cross-sectional study for the cohort of 248 UK patients suggest a similar proportion of carboplatin and cisplatin use. In the UK, [redacted].[5] The proportions used in the model are more similar to estimates from The UK National Mesothelioma Audit 2020 in which pemetrexed with carboplatin was the most common regimen used (48%), followed by pemetrexed with cisplatin (20%), in patients who received chemotherapy.[1]

UK clinical experts agreed that both cisplatin and carboplatin are used in combination with pemetrexed across the UK. One expert estimated a roughly equal split between the use of carboplatin and cisplatin but suggested that there is a move towards using carboplatin because it is possibly more effective, faster, and less toxic. Another expert said that he has been using carboplatin exclusively for many years because, although it seems to be equally effective as cisplatin, carboplatin is less toxic and requires fewer resources.

A scenario analysis assuming an equal split between carboplatin and cisplatin was presented in Document B, Table 57. This had a minor impact on the results; the ICER increased by £23.

B15. In the CS, it is stated that *"On failure with first-line treatment of nivolumab + ipilimumab or pemetrexed + cisplatin or carboplatin (i.e., on entry to the PD health state), a proportion of the initial randomised cohort will go on to a subsequent*

treatment". The distribution of subsequent treatments per each trial arm is based on Checkmate-743.

a. Please clarify whether all patients entering the PD state receive subsequent treatment. If it is only a proportion of patients in the PD state that receive subsequent treatment, please provide that proportion and its source and an explanation of how this was incorporated in the modelling; or alternatively perform scenario analyses using this proportion.

Only a proportion of patients in the PD state receive subsequent therapy. The proportion receiving subsequent therapy in each arm was based on the observed proportion of subsequent therapy in Checkmate-743 (as presented in response to A16: 44.2% in the nivolumab + ipilimumab arm and 40.7% in the PDC arm). Clinical experts consulted during the development of the economic model confirmed that these proportions were aligned with clinical expectations. It was expressed that the proportion could potentially be slightly lower in clinical practice, but it was also highlighted that retrospective analyses have shown the proportion receiving 2nd line therapy to be around 50%.[27] Thus, the proportions observed in Checkmate-743 was deemed appropriate and used in the analyses. The data to model proportion of subsequent treatment is implemented in cell G276:H277 on the Tx_related_Costs sheet of the model.

b. Please provide clarification and justification for Table 44 of the CS. Please provide any information that could support the distributions of subsequent treatments and their generalisability to the England NHS, such as expert opinion or other data sets. Please also state for each subsequent treatment modelled whether these are currently used for patients with untreatable unresectable MPM in the England NHS. Please enable a scenario in which the distributions are amended to match England NHS practice (if it differs). In particular:

    a. Please explain whether nivolumab is envisioned to be used in patients with progressed disease (as is modelled).

There is no standard second-line therapy in MPM used in NHS clinical practice, which was confirmed by UK clinical experts (Appendix N). Second-line treatment

options are not well defined because there is no second-line therapy approved for use, and therapies undergoing clinical trials are recommended above any other option according to the British Thoracic Society guidelines.

The submitted label indication for nivolumab + ipilimumab is only for the first-line treatment of unresectable MPM. During the COVID-19 pandemic in the NHS in England, there is the option to give patients with MPM second-line nivolumab monotherapy instead of second-line chemotherapy to reduce the risk of immunosuppression.[15] UK clinical experts confirmed that second-line nivolumab monotherapy was being used in NHS clinical practice currently.

b. Please explain whether re-treatment of patients with nivolumab + ipilimumab is possible (and envisioned in the England NHS). As per Table 44, 2.2% and 0.6% receive re-treatment respectively.

There are two related but distinct concepts – re-treatment and re-challenge. Re-treatment is defined as discontinuation (due to progression, response or an AE) followed by combination IO therapy with no therapy in between. Re-challenge is similar, but instead the patient receives an intervening, non-IO based therapy before another IO. This decision in the NHS would be at clinical discretion (based on the reason for initial discontinuation) if the clinician felt the patient would continue to benefit and also based on access. Available data relating to re-treatment and re-challenge with immunotherapy are limited and exploratory. BMS currently has no available data to support the re-treatment or re-challenge with nivo +/- ipi in thoracic tumours.

c. Please explain whether re-treatment of patients with pemetrexed + cisplatin / carboplatin is possible.

This is supported by real-world data from the CAS registry of patients with unresectable MPM in England from January 2013-December 2017. Results showed that among 3,159 patients who received first-line therapy, 784 (25.2%) received a second-line therapy during the study period: of these, 43.6% received second-line PDC (platinum + pemetrexed), 18.6% received second-line treatment in a clinical trial, and 24.1% received second-line vinorelbine.[2]

UK clinical experts confirmed that some patients who had a lasting PFS benefit from first line pemetrexed + cisplatin / carboplatin will be offered the same treatment upon progression. Evidence for re-challenge with pemetrexed + cisplatin / carboplatin is available from Italian centres.[28]

d. Please clarify why ipilimumab and pembrolizumab were included in the nivolumab + ipilimumab arm despite them only being used by <1% of patients, and the company's statement that *"Four subsequent treatment strategies were omitted because of low usage (< 1%)".* Consider either including the four other subsequent treatments or also excluding the two further treatments with <1% patient use for consistency.

Subsequent treatments received by at least 1% of patients in either treatment arm were included in the model; only treatments used in less than 1% of patients in both treatment arms were excluded. Ipilimumab and pembrolizumab were received by more than 1% of patients in the pemetrexed + cisplatin / carboplatin arm; therefore, these treatments were included for the nivolumab + ipilimumab arm.

B16. Subsequent treatment duration is 1.7 months regardless of treatment used and stated to be based on Waterhouse et al, 2019. Post-progression survival in the nivolumab + ipilimumab arm is prolonged compared to the comparator arm (as per modelled outcomes).

a. Please provide further justification, for example expert opinion, for the plausibility of the assumption of equal subsequent treatment duration regardless of initial treatment allocation and irrespective of which subsequent treatment is used.

Real-world data from the CAS registry of patients with unresectable MPM in England from January 2013-December 2017 showed that the median treatment duration of second-line therapy was 1.6 months[2], which is in alignment with the 1.7 month duration reported by Waterhouse et al.[29].

Using the same treatment duration regardless of subsequent treatment was a simplifying assumption in the model based on the available data. Accurately accounting for different subsequent treatment durations in the model would have

been difficult because a) subsequent treatment use was available for individual treatments from CheckMate-743 but not for treatment regimens, and b) treatment duration data were not available for the different subsequent treatments. The equal duration of second-line therapy was a conservative assumption because immunotherapies would be expected to have a longer duration of treatment compared with chemotherapies, and there was a higher proportion of subsequent immunotherapies in the PDC arm. Therefore, if treatment duration data were available for each treatment, the subsequent therapy cost for the PDC arm would likely be higher than is currently predicted.

b. Please enable in the model a scenario, and provide results here, in which subsequent treatments and durations are set equal in order to assess the impact of identical subsequent treatment costs on overall model outcomes.

We have performed additional scenario analyses to explore the impact of different assumptions for subsequent treatment use and durations. The results of the scenarios are presented in Table 30.

Table 30. Incremental scenario analysis results of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin in first-line unresectable MPM

Technologies	Total costs (£)	Total LYGs	Total QALYs	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per QALY, £
Scenario 1: PDC subsequent treatment proportions assumed equal to nivolumab + ipilimumab							
Nivolumab + ipilimumab	xxxxxx	xxxxxx	xxxxxx				
Pemetrexed + cisplatin or carboplatin	xxxxxx	xxxxxx	xxxxxx	54,808	0.916	0.702	78,087
Scenario 2: nivolumab + ipilimumab subsequent treatment proportions assumed equal to PDC							
Nivolumab + ipilimumab	xxxxxx	xxxxxx	xxxxxx				
Pemetrexed + cisplatin or carboplatin	xxxxxx	xxxxxx	xxxxxx	54,417	0.916	0.702	78,118
Scenario 3: mean duration of all subsequent treatments increased to 3 months							
Nivolumab + ipilimumab	xxxxxx	xxxxxx	xxxxxx				
Pemetrexed + cisplatin or carboplatin	xxxxxx	xxxxxx	xxxxxx	54,160	0.916	0.702	77,164

Technologies	Total costs (£)	Total LYGs	Total QALYs	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per QALY, £
Scenario 4: mean duration of subsequent nivolumab and ipilimumab increased to 5 months							
Nivolumab + ipilimumab	xxxxxx	xxxxxx	xxxxxx				
Pemetrexed + cisplatin or carboplatin	xxxxxx	xxxxxx	xxxxxx	53,510	0.916	0.702	76,238

Inc = Incremental; LYG = life-year gained; QALY = quality-adjusted life-year.

Results and uncertainty analyses

B17. Base-case results

a. Please provide a disaggregated overview of the results, i.e. per health state and treatment for

    a. life years (LYs),

    b. QALY and

    c. costs (distinguishing between treatment costs, health state costs, adverse event costs).

All the requested disaggregated results were provided in Document C, Appendix L.

b. Please provide a comparison of the observed survival as well as progression free survival (e.g. using restricted mean survival time; RMST) and the undiscounted LY as well as undiscounted progression free LY (estimated in the model) and elaborate on the plausibility of the differences.

Table 31 presents a comparison of the observed and modelled overall survival outcomes. Table 32 presents a comparison of the observed and modelled progression-free survival outcomes.

Restricted mean survival time was not reported in CheckMate-743. Median survival has been presented, along with absolute survival at different timepoints. The modelled survival outcomes are closely aligned with the observed outcomes.

Table 31. Observed and Modelled OS

Dataset	Curve	Absolute survival, %								Median (mos)	Mean (mos)
		6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 15	Yr 20		
Nivolumab + ipilimumab											
CheckMate 743	Kaplan-Meier	84.0	67.9	40.8	23.3	-	-	-	-	18.10	-
Model prediction	Piecewise log-logistic	84.0	67.9	39.3	26.3	14.4	5.7	3.2	1.9	17.94	34.42
Pemetrexed + cisplatin/carboplatin											
CheckMate 743	Kaplan-Meier	82.2	57.7	27.0	15.2	-	-	-	-	14.10	-
Model prediction	Piecewise exponential	82.2	57.7	28.7	15.9	4.9	0.3	0.0	0.0	14.03	20.61

OS: Overall survival; Yr: Year; Base case curve in bold.

Table 32. Observed and Modelled PFS

Dataset	Curve	Absolute survival (%)								Median (mos)	Mean (mos)
		6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 15	Yr 20		
Nivolumab + ipilimumab											
CheckMate 743	Kaplan-Meier	52.1	30.2	16.3	11.9	-	-	-	-	6.77	-
Model prediction	Generalized gamma	50.4	30.7	16.8	11.4	6.7	3.2	2.0	1.4	5.98	18.51
Pemetrexed + cisplatin/carboplatin											
CheckMate 743	Kaplan-Meier	61.9	23.8	7.2	0.0	-	-	-	-	7.20	-
Model prediction	Log-logistic	62.1	25.6	6.7	2.8	0.9	0.2	0.1	0.0	7.36	10.51

Mos: Months; PFS: Progression-free survival; Yr: Year; base case in bold.

c. Regarding the model estimated differences in LYs and QALYs between the intervention and the comparator; please provide an explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence (NICE DSU TSD 19 recommendation 13).

The partitioned survival model approach generates the time spent in each model health state based on the PFS and OS curves for the intervention and comparator.

Time spent in the progression free health state is calculated using the area under the PFS curve, and time spent in the progressed health state is calculated as the difference between the OS and PFS curves. Treatment-specific utility weights are applied to each health state to generate QALYs for the intervention and comparator. The division of health states based on disease progression aligns with the clinical pathway and allows for important differences in patient HRQOL to be captured.

The estimated LYs and QALYs are calculated based on health-state occupancy, which is governed by the underlying PFS and OS curves. Justification for the methodology and plausibility of the survival extrapolations has been provided in response to questions B5 and B8.

Validation

B18. Please provide any detail on internal validation exercises performed, for example by completing the TECH-VER checklist (Büyükkaramikli et al, 2019 (**https://pubmed.ncbi.nlm.nih.gov/31705406/**)

During the development of the economic model, external clinical and health economic experts were consulted to ensure an appropriate approach was taken and that the model had clinical validity. This included the following (meeting notes are included in Appendix N):

- A UK clinical advisory board meeting was held on 10 September 2020. Eight UK consultant oncologists, one UK consultant oncology nurse, and one UK consultant thoracic pathologist were included in the discussions.
- HTA advisory meetings were held in November 2020. Two consultant medical oncologists from large NHS oncology centres in England were included in the discussions.
- A global economic advisory board was held in November 2020 and included UK health economists and UK clinicians.

Furthermore, the model was quality controlled and all calculations and data were checked by an independent researcher.

B19. Please provide cross validations, i.e. comparisons with other relevant NICE TAs focussed on similar, potentially relevant, diseases (e.g. TA 135, and others?) and elaborate on the identified differences regarding:

a. Model structure and assumptions

b. Input parameters related to:

    a. Clinical effectiveness

    b. Health state utility values

    c. Resource use and costs

c. Estimated outcomes per comparator/ intervention

    a. Life years

    b. QALYs

    c. Costs

TA135[18] was published in 2008, since NICE methods and process have changed since then, we do not think it is appropriate for use in validation. Further, although no new treatments have been approved since 2008, other elements of care that may impact outcomes and decision-making have changed.

B20. Please assess the external validity of the estimated (intermediate) outcomes with data used to develop the model and also other data not used to develop the model.

As reported in the CS and throughout this response, external clinical data have been used extensively to validate the model predictions. For example, see section B3.3 in the CS and responses to questions B6 and B7 in this document.

References

1. Royal College of Physicians. National mesothelioma audit report 2020 (for the audit period 2016-18). May 2020. Available at: https://www.rcplondon.ac.uk/projects/outputs/national-mesothelioma-audit-report-2020-audit-period-2016-18. Accessed 10 August 2020.
2. Baas P, Daumont MJ, Lacoin L, Penrod J, Carroll R, Tanna N. Treatment patterns and outcomes in malignant pleural mesothelioma in England: a nationwide CAS registry analysis from the I-O Optimise initiative [poster 1909P]. Presented at the European Society for Medical Oncology Virtual Congress; 19-21 September 2020.
3. Woolhouse I, Bishop L, Darlison L, De Fonseka D, Edey A, Edwards J, et al. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. Thorax. 2018 Mar;73(Suppl 1):i1-i30.

4. Baas PD, MJ; Lacoin, L; Penrod, JR; Carroll, R; Venkatesan, S; Ubhi, H; Calleja, A; Snee, M. . Treatment patterns and outcomes for patients with malignant pleural mesothelioma in England in 2013–2017: A nationwide CAS registry analysis from the I-O Optimise initiative. . Manuscript in preparation. 2021.
5. Moore AB, B; Hart, K; McDonald, L; McKenna, M; Daumont, MJ Malignant Pleural Mesothelioma: Treatment Patterns and Humanistic Burden of Disease in Europe. . Manuscript in preparation. 2021.
6. Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet. 2021 Jan 21.
7. Santoro A, O'Brien ME, Stahel RA, Nackaerts K, Baas P, Karthaus M, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaïve patients with malignant pleural mesothelioma: results of the International Expanded Access Program. J Thorac Oncol. 2008 Jul;3(7):756-63.
8. Bristol-Myers Squibb. Press release: U.S. Food and Drug Administration Approves Opdivo® (nivolumab) + Yervoy® (ipilimumab) as the first and only immunotherapy treatment for previously untreated unresectable malignant pleural mesothelioma. 2 October 2020. Available at: https://investors.bms.com/iframes/press-releases/press-release-details/2020/U.S.-Food-and-Drug-Administration-Approves-Opdivo-nivolumab--Yervoy-ipilimumab-as-the-First-and-Only-Immunotherapy-Treatment-for-Previously-Untreated-Unresectable-Malignant-Pleural-Mesothelioma/default.aspx. Accessed 12 November 2020.
9. NICE. Technology appraisal guidance [TA655]: nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy National Institute for Health and Care Excellence; 21 October 2020. Available at: https://www.nice.org.uk/guidance/ta655. Accessed 26 November 2020.
10. NICE. Nivolumab for previously treated non-squamous non-small-cell lung cancer [TA484]. National Institute for Health and Care Excellence; 2017. Available at: https://www.nice.org.uk/guidance/ta484. Accessed 9 July 2018.
11. Tsao A, et al. Evaluation of flat dosing for nivolumab + ipilimumab in first-line unresectable malignant pleural mesothelioma: CheckMate-743. Poster presented at the ESMO Immuno-Oncology Virtual Congress 2020: December 9–12: 2020. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-immuno-oncology-virtual-congress-2020/evaluation-of-flat-dosing-for-nivolumab-nivo-ipilimumab-ipi-in-first-line-1l-unresectable-malignant-pleural-mesothelioma-mpm-checkmate-7. Accessed 8 Feb 2021.
12. Bristol-Myers Squibb. Nivolumab + ipilimumab: final clinical study report for study CA209743. 3 August 2020.
13. Hotta K, Fujimoto N. Current evidence and future perspectives of immune-checkpoint inhibitors in unresectable malignant pleural mesothelioma. J Immunother Cancer. 2020;8(1):e000461.
14. Fennell Dea. Nivolumab Versus Placebo in Relapsed Malignant Mesothelioma: Preliminary results from the CONFIRM Phase 3 Trial. Presented at WCLC Singapore: January 28-31 2021.
15. NICE/NHS England. NG161 NHS England interim treatment options during the COVID-19 pandemic. National Institute for Health and Care Excellence/National Health Service England; 22 October 2020. Available at:

https://www.nice.org.uk/guidance/ng161/resources/nhs-england-interim-treatment-options-during-the-covid19-pandemic-pdf-8715724381. Accessed 26 October 2020.
16. Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, et al. Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation. Health Technol Assess. 2007 Jan;11(1):1-90.
17. Liverpool Reviews and Implementation Group. Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation. 1 December 2005. Available at: https://www.nice.org.uk/guidance/ta135/documents/assessment-report2. Accessed 26 August 2020.
18. NICE. Technology appraisal guidance [TA135]: pemetrexed for the treatment of malignant pleural mesothelioma. National Institute for Health and Care Excellence; 23 January 2008. Available at: https://www.nice.org.uk/guidance/ta135. Accessed 25 September 2020.
19. SMC. Pemetrexed 500mg infusion (Alimta®) No. (192/05). Scottish Medicines Consortium; 2005. Available at: https://www.scottishmedicines.org.uk/media/2151/pemetrexed_500mg_infusion__alimta___192-05_.pdf. Accessed 13 January 2021.
20. Woods B, Sideris E, Palmer S, Latimer N, M. S. NICE DSU technical support document 19. Partitioned survival analysis for decision modelling in health care: A critical review. 2017. Available at: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf. Accessed 9 November 2020.
21. Briggs A, Baker TM, Gilloteau I, Orsini L, Wagner S, Paly V. Partitioned Survival Versus State Transition Modeling in Oncology: a Case Study with Nivolumab in Advanced Melanoma. Value in Health. 2015 11/01;18:A338.
22. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet. 2016 Apr 2;387(10026):1405-14.
23. Klijn SL, Fenwick E, Kroep S, Johannesen K, Malcolm B, Kurt M, et al. What Did Time Tell Us? A Comparison and Retrospective Validation of Different Survival Extrapolation Methods for Immuno-Oncologic Therapy in Advanced or Metastatic Renal Cell Carcinoma. PharmacoEconomics. 2021 2021/01/11.
24. Antonia SJ, Borghaei H, Ramalingam SS, Horn L, De Castro Carpeno J, Pluzanski A, et al. Four-year survival with nivolumab in patients with previously treated advanced non-small-cell lung cancer: a pooled analysis. Lancet Oncol. 2019 Oct;20(10):1395-408.
25. Bristol-Myers Squibb. Analyses of quality of life endpoints in CA209743 (CheckMate 743), a phase 3, randomized, open-label trial of nivolumab in combination with ipilimumab versus pemetrexed with cisplatin or carboplatin as first line therapy in unresectable pleural mesothelioma. 17 November 2020.
26. Baas P. First-line nivolumab + ipilimumab vs chemotherapy in unresectable malignant pleural mesothelioma: CheckMate 743 [oral presentation]. Presented at the World Conference on Lung Cancer Virtual Presidential Symposium; 8 August 2020.
27. Raynaud C, Greillier L, Mazieres J, Monnet I, Mastroianni B, Robinet G, et al. Management of malignant pleural mesothelioma: a French multicenter

retrospective study (GFPC 0802 study). BMC Cancer. 2015 2015/11/06;15(1):857.
28. Bearz A, Talamini R, Rossoni G, Santo A, de Pangher V, Fasola G, et al. Re-challenge with pemetrexed in advanced mesothelioma: a multi-institutional experience. BMC research notes. 2012;5:482-.
29. Waterhouse D, Nwokeji E, Boyd M, Penrod JR, Espirito J, Robert NJ, et al. Treatment patterns and outcomes of advanced malignant pleural mesothelioma (MPM) patients in a community practice setting [poster]. Presented at the International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer; 7-10 September 2019. Barcelona, Spain.

NICE National Institute for Health and Care Excellence

Patient Organisation Submission

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID 1609]

Thank you for agreeing to give us your organisation's views on this technology and its possible uses in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question - they are prompts to guide you. The text box will expand as you type. [Please note that the declarations of interest relevant to this topic are compulsory].

Information on completing this submission.

- Please do not embed documents (such as PDF) in a submission because these may lead to the information being mislaid or make the submission unreadable.
- We are committed to meeting the requirements of copyright legislation. If you intent to include **journal articles** in your submission, you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should be no longer than 10 pages.

About you	
1. Your Name	[redacted]
2. Name of Organisation	Mesothelioma UK
3. Job Title or Position	[redacted]
4a. Brief description of the organisation (including who it funds). How many members does it have?	Mesothelioma UK is a national specialist resource centre, specifically for the asbestos-related cancer, mesothelioma. The charity is dedicated to providing specialist mesothelioma information, support and education, and to improving care and treatment for all UK mesothelioma patients and their carers. The charity integrates into NHS front line services to ensure specialist mesothelioma nursing is available at the point of need. This is achieved through a growing network of specialist mesothelioma nurses, regionally based in NHS hospitals funded by Mesothelioma UK. Our vision is:

	• To be an essential one stop shop for up to date mesothelioma support, information and education. • Support the NHS to drive standards and ensure equitable access to world class treatment, trials and care. • To help the UK to lead the way in making mesothelioma history through world class audit, research and clinical trials, • To raise the profile of mesothelioma to help prevent future cases of asbestos related disease. Funding is provided from voluntary donations, legacies, fundraising, online shopping, grants and sponsorship from a panel of legal firms.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and / or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix]. Is so, please state the name of the manufacturer, amount, and purpose of funding.	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	• Mesothelioma Information line 0800 169 2409 (Mon to Fri 8.30 – 4.30) • Clinical Nurse Specialists (CNS) spoke to patients and recorded the views expressed • Newsletter • Support Groups • Website / email • Social Media (Facebook, Twitter, Instagram) • Feedback • Patient and Carer Day • Advocacy at Education events
Living with the Condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Research Paper**: **Living well with Cancer** **Findings**: People with Malignant Pleural Mesothelioma (MPM), along with family members, work hard together to move from a period of distress at the time of diagnosis through to finding ways of living well. They do this whilst accommodating the effects of ill health. The following key themes emerged; 1) finding focus for hope, 2) accessing support, 3) learning how to support physical wellbeing and 4) planning ahead.

Recommendations: Several recommendations were generated about how health professionals can assist people to live well with MPM. The recommendations include recognising and communicating reasons for hope, accessing support, promoting wellbeing and encouraging people to plan ahead to maintain control over decisions. Consultation with representatives of the three participant groups could help to develop a plan to implement the recommendations.

Conclusions: The experiences of people in this study provide messages for future patients and carers and health professionals on how to live well' with MPM. Nurse specialists are ideally placed to support this process. Further research is needed about how people who have less social support and who feel hopeless can be supported to live well.

- **MORE Report**

This report provides an insight into the findings from Mesothelioma UK's Mesothelioma Outcomes Research and Experience (MORE). MORE received over 500 responses from people living with mesothelioma. Each responder provided information about their clinical circumstances, their experience of care and their current quality of life. MORE is Mesothelioma UK's second patient experience survey. Responses from 503 patients from across the UK were included in the final analysis. The survey highlights confidence and satisfaction across many areas but it has also revealed a number of interesting findings that Mesothelioma UK hopes to address over the coming months and years.

Appointment and Admissions: Unfortunately, 9% (44) of responders visited their GP 5 or more times before being referred to hospital for further tests. 26% (129) attended hospital in excess of 20 times over the last year for tests, outpatients' appointments or treatment. 9% (44) had been admitted to hospital 5 or more times in the last year. 31% (89) had shared care between different hospitals. 64% (323) had 3 or more CT scans in the last year. 10% (48) had attended another hospital for a second opinion many having travelled more than 2 hours to achieve this.

Managing Symptoms: Pain (62%/308), breathlessness (64%/318), cough (41%/204) and fatigue (64%/319) were all experienced. Help given to control pain and breathlessness scored high (99% & 93%) but responders felt not everything was done to help control fatigue and cough (16% & 21%). 16% (58) of the 367 people that described needing fluid drainage had this done 5 or more times. 32% (116) were offered an indwelling drain and 18% (67) had one.

Communication and Support: 27% (135) felt being told their diagnosis could have been given more sensitively. 9% (43) had received some end of life planning support. 27% (136) were informed about the role of the coroner / procurator fiscal. 5% (24) were not given information about how to get financial help. For 40% (191) the cost of travel insurance had been an issue. 23% (116) are expecting to have to pay for private treatment.

Treatment and Trials: 17% (83) of responders had a surgical resection aimed at removing some or all of the tumour 77% (387) had chemotherapy, 9% (46) had radiotherapy, 11% (55) immunotherapy. 11% (41) of responders who received systemic anti-cancer treatment went on to have at least 3 lines of treatment 71% (358) had clinical trials discussed with them and 34% (171) had been enrolled in a clinical trial.

- **Checkmate 793 Trial**

The trial evaluating nivolumab in combination with ipilimumab in previously untreated malignant pleural mesothelioma met its primary endpoint of overall survival.

The CheckMate-743 trial evaluating nivolumab (Opdivo) in combination with ipilimumab (Yervoy) in previously untreated malignant pleural mesothelioma met its primary endpoint of overall survival (OS), according to Bristol-Myers Squibb, the agent's developer.[1]

Based on a pre-specified interim analysis conducted by an independent data monitoring committee, the combination treatment was also found to result in a statistically significant and clinically meaningful improvement in OS compared to chemotherapy (pemetrexed and cisplatin or carboplatin). Additionally, the safety profile of nivolumab plus ipilimumab observed in the trial reflects the known safety profile of the combination.

"Malignant pleural mesothelioma is a devastating disease that has seen limited treatment advances over the past decade," Sabine Maier, MD, development lead of thoracic cancers at Bristol Myers Squibb, said in a press release. "These topline results from the CheckMate-743 trial demonstrate the potential of Opdivo plus Yervoy in previously untreated patients with malignant pleural mesothelioma and is another example of the established efficacy and safety of the dual immunotherapy combination seen in multiple tumour types."

"We would like to thank the patients who participated in this trial, as well as the investigators and site personnel for their perseverance during the conduct of this study and in delivering this important result for patients in the midst of the COVID-19 pandemic," Maier added. "We look forward to working with investigators to present the results at a future medical meeting, and to discussing them with health authorities."

Overall, 606 participants with unresectable pleural mesothelioma were randomized to either nivolumab plus ipilimumab or pemetrexed plus cisplatin or carboplatin. Patients randomized to the nivolumab plus ipilimumab combination were administered 3 mg/kg of nivolumab every 2 weeks and 1 mg/kg of ipilimumab every 6 weeks.[2]

Secondary endpoints for the trial included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and efficacy measures according to PD-L1 expression level.

	In the single-center, single-arm, phase II INITIATE trial researchers assessed nivolumab plus ipilimumab in patients with malignant pleural mesothelioma who progressed after at least 1 line of platinum-containing chemotherapy. The study enrolled patients between October 5, 2016, and August 3, 2017. Participants were administered 240 mg of nivolumab every 2 weeks and 1 mg/kg of ipilimumab every 6 weeks up to 4 times. Only 34 of the 38 enrolled patients were evaluable for response assessment at 12 weeks, with 10 (29%) achieving a partial response and 13 (38%) demonstrating stable disease. This resulted in an overall disease control rate of 68% (95% CI, 50-83). Notably, treatment-related adverse events (AEs) were reported in 33 (94%) patients. The most AEs were infusion-related reactions, skin disorders, and fatigue. Further, grade 3 treatment-related AEs were reported in 12 (34%) of 35 patients. References: 1. Bristol Myers Squibb Announces Positive Topline Result from Pivotal Phase 3 Trial Evaluating Opdivo (nivolumab) plus Yervoy (ipilimumab) vs. Chemotherapy in Previously Untreated Malignant Pleural Mesothelioma. Published April 20, 2020. news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-announces-positive-topline-result-pivotal. Accessed April 20, 2020. 2. Disselhorst MJ, Quispel-Janssen J, Lalezari F, et a. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. *Lancet*. doi:10.1016/S2213-2600(18)30420-X.
Current Treatment of the Condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The phase III CheckMate 743 trial of Ipilumumab and Nivolumab has broken new ground for patients with malignant pleural mesothelioma (MPM) compared with current treatments available to them on the NHS by establishing the benefit of a chemotherapy-free regimen in patients with previously untreated disease. This is the first positive randomized trial of dual immunotherapy in first-line treatment of patients with unresectable MPM and patients welcome this. Therefore nivolumab plus ipilimumab should be considered as a new standard of care and patients should have access to this treatment without having to provide funding on a private basis from funding which may be accessed from their compensation claims.

8. Is there an unmet need for patients with this condition?	Yes, there is currently no cure for Mesothelioma. Other modality treatments than chemotherapy should be pursued. These developments may lead to extending life expectancy and assisting with the burden of disease which mesothelioma patients face.
Advantages of the Technology	
9. What do patients or carers think are the advantages of technology?	Patient 1. "An opportunity to receive proven life extending treatment. For many patients the treatment offers a return to a near normal healthy standard of life. Many patients are subsequently able to focus on post cancer wellness and fitness". "My treatment side effects were fairly minimal. On many occasions i took advantage of the hospital being so near to the airport that i would catch a flight to the Canary or Baleric Islands for short cycling breaks". Patient 2 "I was diagnosed with mesothelioma in April 2019, unfortunately chemotherapy had no effect at all as a treatment. I entered a trial on the NHS which helped initially but the cancer started to grow again. I have received 14 cycles of Ipilimumab and Nivolumab treatment and have had two CT scans which have both shown a progressive improvement in the mesothelioma. The side effects are minimal for me and do not affect my daily life. I would highly recommend this treatment for mesothelioma sufferers and would like to see this made available on the NHS."
Disadvantages of the Technology	
10. What do patients or carers think are disadvantages of the technology?	Patient 1. "My treatment was at the Western General Hospital Edinburgh. Fortnightly infusions with 6 weekly CT scans. The CT scans did not coincide with treatment days. The hospital is a round drive trip of 6 hours. This made for long days. Given the so far outcome of the treatment and trial the travel was not a significant problem. Although I could imagine patients without close support such travel would not be possible. Of course treatment at a local hospital would have been ideal. Towards the end of treatment i had symptoms of Colitis and then later on more seriously i was hospitalised with a pancreatic condition. The Colitis cleared up almost immediately after ceasing treatment. The pancreatic condition to took a long course of steroids in which i lost muscle mass". Patient 1. "Not everyone responds to treatment in a positive way. There can be pancreatic side effects. Pancreas amylase levels will need to be monitored closely". Patient 2 "The funds were available to me through an industrial disease claim to access mesothelioma treatment privately" .

Patient Population	
11. Are there any groups of patients who might benefit more or less from the technology than others, if so, please describe them and explain why?	• The Checkmate 743 trial suggest patients with non-epithelioid mesothelioma seem to have a better response to the technology. Research has shown non-epithelioid mesothelioma to be the most aggressive, giving a higher symptom burden, having fewer treatment options and a shorter prognosis of only a matter of a few months. • Patients who are not able to self fund or pay for treatment from funding from a compensation claim are at a disadvantage.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	If the technology only becomes available in the setting of private / self funding an inequality will be generated and should be ethically questioned.
Other Issues	
13. Are there any other issues that you would like the committee to consider?	No

14. **To be added by technical team** at scope sign off. [Note that topic specific questions will be added only if the treatment pathway or likely use of technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal]. If there are none delete highlighted rows and renumber below.	
Key Messages	
15. In up to five bullet points please summaries the key messages of your submission.	• The phase III CheckMate 743 trial of Ipilumumab and Nivolumab has broken new ground for patients with malignant pleural mesothelioma (MPM) compared with current treatments available to them on the NHS by establishing the benefit of a chemotherapy-free regimen in patients with previously untreated disease. • This is the first positive randomized trial of dual immunotherapy in first-line treatment of patients with unresectable MPM and patients welcome this. • Therefore nivolumab plus ipilimumab should be considered as a new standard of care and patients should have access to this treatment without having to provide funding on a private basis from funding which may be accessed from their compensation claims. • Generally the side effects of the technology experienced by patients were fairly minimal compared with chemotherapy. However, expertise is required in the planning, treatment and monitoring of the patients having this technology .

Thank you for your time.

Please log into your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Your Privacy

The information you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if would like to receive information about other NICE topics.

For more information about how we process your personal data, please see our privacy note.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**ROYAL COLLEGE OF PATHOLOGISTS** University hospital of wales (employer)

3. Job title or position	
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**ROYAL COLLEGE OF PATHOLOGISTS – CHARITY-CREDENTIALING BODY FOR PATHOLOGISTS IN UK**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**NOT TO MY KNOWLEDGE**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NO**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	TO IMPROVE DISEASE FREE INTERVAL, OVERALL MORTALITY AND DECREASE MORBIDITY
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	BEYOND THE SCOPE OF A PATHOLOGIST

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	YES
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	THIS IS SUBJECT TO CLINICAL FACTORS, AGE, ANATOMICAL SITE, DISEASE TYPE, TUMOUR GRADE AND STAGE
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	YES, BTS GUIDELINES
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	NO

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	PROVIDE CLARITY
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	YES
• How does healthcare resource use differ between the technology and current care?	N/A TO PATHOLOGY
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	N/A TO PATHOLOGY
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	N/A TO PATHOLOGY

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	N/A TO PATHOLOGY
• Do you expect the technology to increase length of life more than current care?	N/A TO PATHOLOGY
• Do you expect the technology to increase health-related quality of life more than current care?	N/A TO PATHOLOGY
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	N/A TO PATHOLOGY
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	N/A TO PATHOLOGY
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	N/A TO PATHOLOGY
15. Do you consider that the use of the technology will result in any substantial health-	YES, POTENTIALLY, EVIDENCE IS SUPPORTIVE FROM US STUDY

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	YES
• Is the technology a 'step-change' in the management of the condition?	POTENTIALLY FOR A SELECTIVE NUMBER OF PATIENTS
• Does the use of the technology address any particular unmet need of the patient population?	N/A TO PATHOLOGY

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	N/A TO PATHOLOGY
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	N/A TO PATHOLOGY
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	N/A TO PATHOLOGY
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	N/A TO PATHOLOGY

21. How do data on real-world experience compare with the trial data?	N/A TO PATHOLOGY
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	NO
22b. Consider whether these issues are different from issues with current care and why.	N/A TO PATHOLOGY
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains	

uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- THE DIAGNOSIS OF MALIGNANT MESOTHELIOMA IS PROBLEMATIC ESPECIALLY IN SMALL BIOPSIES AND IN THE PERITONEUM
- IT IS ESSENTIAL TO OBTAIN AN ACCURATE PATHOLOGY DIAGNOSIS – THERE IS LIMITED EXPERIENCE BY MANY PATHOLOGISTS WHEN DIAGNOSING MESOTHELIOMA AND DISTINGUISHING IT FROM OTHER NEOPLASMS
- ENTRY SHOULD BE SUPPORTED BY CONFIRMATORY DIAGNOSIS BY A RECOGNISED EXPERT IN MESOTHELIOMA DIAGNOSIS
- A CLEAR DIAGNOSTIC ALGORITHM SHOULD BE ADHERED TO AS OUTLINED IN PRESENTATION ALONG GUIDELINES OF THE INTERNATIONAL MESOTHELIOMA PANEL
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Authors
Nigel Armstrong, Health Economist, KSR Ltd
Sabine Grimm, Health Economist, Maastricht UMC, the Netherlands
Bram Ramaekers, Health Economist, Maastricht UMC, the Netherlands
Marie Westwood, Reviews Manager, KSR Ltd
Annette Chalker, Systematic Reviewer, KSR Ltd
Mohammed Islam, Health Economist, KSR Ltd
Gill Worthy, Statistician, KSR Ltd
Shelley De Kock, Information Specialist, KSR Ltd
Manuela Joore, Health Economist, Maastricht UMC
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to
Nigel Armstrong, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, United Kingdom
YO19 6FD

Date completed 17/03/2021

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number STA 13/30/12.

Declared competing interests of the authors

None.

Acknowledgements

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Armstrong N, Grimm S, Ramaekers B, Westwood M, Chalker A, Islam M, Worthy G, De Kock S, Joore MA, Kleijnen J. Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2021.

Contributions of authors

Nigel Armstrong acted as project lead, systematic reviewer and health economist on this assessment, critiqued the clinical effectiveness methods and evidence and the company's economic evaluation and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers and Mohammed Islam acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Marie Westwood and Annette Chalker acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Shelley De Kock critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
ASBI	Average Symptom Burden Index
AST	Aspartate aminotransferase
BCS	Best case scenario
BI	Budget impact
BIC	Bayesian information criterion
BICR	Blinded independent central review
BMJ	British Medical Journal
BMS	Bristol-Myers Squibb
BTS	British Thoracic Society
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTR	Clinical trial results
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions 3 levels
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FAD	Final appraisal document
FDA	Food and Drug Administration
GHS	Global health status
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
IC	Investigator choice
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost effectiveness ratio
IHC	Immunohistochemistry
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier

KSR	Kleijnen Systematic Reviews
LCSS Meso	Lung Cancer Symptom Scale–Mesothelioma
LYs	Life years
LYG	Life years gained
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MOS SF-36	Medical Outcomes Study Short Form Survey
MPM	Malignant pleural mesothelioma
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PDC	Platinum doublet chemotherapy
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PH	Proportional hazards
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partition survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q3W	Every three weeks
QALY	Quality-adjusted life year
QLQ-C30	Quality of Life Questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Relative risk; Risk ratio
SAE	Serious adverse events
SC	Subcutaneous
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single technology appraisal
STM	State transition model
TA	Technology assessment
TEAE	Treatment emergent adverse events

TRAE	Treatment-related adverse event
TSD	Technical Support Document
UK	United Kingdom
UMC	University Medical Centre
VAS	Visual analogue scale

Table of Contents

Table of Tables

Table of Figures

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary in presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see Sections 2 (background), 3 (decision problem), 4 (clinical effectiveness) and 5 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report sections
1	Effectiveness and safety of expected nivolumab fixed dosing	Section 2.2
2	Applicability of comparator to English NHS practice	Section 2.3
3	Immaturity of CheckMate-743 trial outcomes	Section 3.2.4
4	Subsequent therapy: difference between arms and applicability to English NHS practice	Section 3.2.4
5	Subgroup effectiveness of nivolumab + ipilimumab according to PD-L1 status and histology	Section 3.2.5
6	Model structure - the use of a PSM, without a STM approach to verify the results	Section 4.2.2
7	Population – no subgroup cost effectiveness analyses presented	Section 4.2.3
8	Intervention & comparators – two-year stopping rule may not be completely adhered to in trial	Section 4.2.4
9	Treatment effectiveness and extrapolation – immaturity of the long-term PFS and OS data	Section 4.2.6
10	Health-related quality of life – duration of utility benefits for nivolumab + ipilimumab	Section 4.2.8
11	Resources and costs – estimation of time to treatment discontinuation	Section 4.2.9
12	Resources and costs – uncertainty about subsequent treatments	Section 4.2.9
13	Resources and costs – adverse events	Section 4.2.9
14	Company's cost effectiveness results – proportion of PF LYs accumulated beyond the observed data	Section 5.1

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are matters of judgement relating to the effectiveness and relative effectiveness of nivolumab + ipilimumab versus platinum doublet chemotherapy (PDC) (regarding overall survival (OS) and progression-free survival (PFS)) and the long-term impact on health-related quality of life

(HRQoL). Further differences are in the estimation of costs regarding assumptions about time on treatment, subsequent treatments and adverse events (AEs).

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (OS) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased mean PFS (undiscounted time in the progression-free (PF) health state: [redacted] months) and mean OS (undiscounted survival: [redacted] months) compared with PDC.
- Increased health state utility values for the PF (0.74 vs 0.73) and PD (0.65 vs 0.58) health states compared with PDC.
- The PFS, OS and health state utility benefits are maintained for the whole duration of the time horizon (i.e. no waning of these treatment benefits).

Overall, the technology is modelled to affect costs by:

- its higher unit price than PDC prices
- cost-savings through delayed more severe health state costs and subsequent treatment costs
- potentially less costly subsequent treatments (uncertain) and potentially AEs (direction uncertain).

The modelling assumptions that have the greatest effect on the ICER are:

- treatment waning from five years onwards
- using the log-logistic distribution for estimating OS in the PDC arm
- using time to discontinuation (TTD) estimates with 100% dose intensity instead of the number of mean doses approach.

1.3 The decision problem: summary of the ERG's key issues

The ERG is reasonably satisfied that the population, which includes Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1, as specified in the decision problem matches that in the CheckMate-743 trial and, although narrower than that in the scope, is appropriate. The ERG is also satisfied that this narrower population is consistent with the omission of best supportive care (BSC) as a comparator. The company have also provided evidence sufficient to support the exclusion of raltitrexed as a relevant comparator for the National Health Service (NHS) in England. This leaves two remaining key issues, shown in Tables 1.2 and 1.3.

Table 1.2: Key issue 1 Effectiveness and safety of expected nivolumab fixed dosing

Report section	Section 2.2
Description of issue and why the ERG has identified it as important	The effect of fixed dosing vs. weight-based dosing, as used in CheckMate-743, is uncertain.
What alternative approach has the ERG suggested?	The ERG requested evidence to support the relative efficacy and safety of the two dosing regimens. However, the evidence provided by the company lacked clarity or was not appropriate.
What is the expected effect on the cost effectiveness estimates?	Unknown

Report section	Section 2.2
What additional evidence or analyses might help to resolve this key issue?	The company could provide clarification regarding the analyses that they referred to in the response to clarification. There is also the possibility that further evidence exists that compares the two methods of dosing.

Table 1.3: Key issue 2 Applicability of comparator

Report section	Section 2.3
Description of issue and why the ERG has identified it as important	The extent to which the clinical judgments made as to investigator choice of PDC, i.e. carboplatin or cisplatin, in CheckMate-743 match those that would be made in English NHS practice is uncertain.
What alternative approach has the ERG suggested?	The ERG requested evidence as to the degree of consistency, to which the company responded by providing the proportion of patients in the UK who have received the two platinum-based treatments. However, because there appeared to be considerable variation between sources, the uncertainty remains unresolved.
What is the expected effect on the cost effectiveness estimates?	Unknown, with likely small impact on cost.
What additional evidence or analyses might help to resolve this key issue?	The ERG cannot conceive of a way to reduce the uncertainty and therefore this issue will probably subject to the application of judgment.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The CheckMate-743 trial is a relatively high-quality source of evidence to inform effect estimates for the outcomes listed in the scope for the comparison between nivolumab + ipilimumab and the most appropriate comparators, as explained in Section 1.3. However, there remain two key issues, as shown in Tables 1.4, 1.5 and 1.6.

Table 1.4: Key issue 3 Immaturity of CheckMate-743 trial outcomes

Report section	Section 3.2.4
Description of issue and why the ERG has identified it as important	The only results that have been presented are for an interim analysis with a database lock 3 April 2020.
What alternative approach has the ERG suggested?	The ERG asked for the results from a later data-cut, but the company stated that no further results were available and did not provide a date for their submission.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The uncertainty in all outcomes especially OS and PFS and for subgroups (see Key issue 5) would be reduced considerably by the provision of updated results.

Table 1.5: Key issue 4 Subsequent therapy

Report section	Section 3.2.2
Description of issue and why the ERG has identified it as important	There was a difference in the number of patients taking each type of subsequent therapy between the nivolumab + ipilimumab and PDC arms of CheckMate-743 and, apparently, between the PDC arm and UK clinical experience.
What alternative approach has the ERG suggested?	The ERG requested evidence as to the effect that the differences described above may have and for the comparison with English NHS practice. However, the ERG could not validate the results regarding time survived on subsequent therapy or the nature of that subsequent therapy based on the reference provided.[1] With the FAC, the poster for that reference has now been provided to enable the ERG to validate the figures provided by the company. Nevertheless, the figures for percentage receiving each type of subsequent therapy received in UK clinical practice provided do appear to be quite different to those in the PDC arm of the CheckMate-743 trial.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	It is unlikely that the effect of any difference in subsequent therapy between the trial arms or between the PDC arm and English NHS practice can be estimated with any confidence.

Table 1.6: Key issue 5 Subgroup effectiveness of nivolumab + ipilimumab according to PD-L1 status and histology

Report section	Section 3.25
Description of issue and why the ERG has identified it as important	Subgroup analysis by both PD-L1 status and histology, which was included in the scope, reveals potential variation and in some cases 95% CIs that overlap the point of no difference for nivolumab + ipilimumab versus PDC for both OS and PFS. This is particularly the case for PD-L1<1% where for PFS there is little uncertainty (point estimate for HR greater than 1 and 95% CI does not include 1) that PDC is superior and for OS where there appears to be little difference between groups (95% CI includes 1).
What alternative approach has the ERG suggested?	No alternative approach has been suggested by the ERG other than to provide results from a later data-cut (see Key issue 4).
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Given the current evidence, uncertainty would be reduced by considering analysing the decision problem using combined PD-L1 status and histology subgroups. It would also be reduced by submission of more complete results i.e. at a later data-cut.

1.5 The cost effectiveness evidence: summary of the ERG's key issues

The company's cost effectiveness model was well built and complied with the NICE reference case. The main critique points are modelling choices and assumptions. The overarching challenge was the immaturity of the data from CheckMate-743, which results in the ICER being very uncertain. A full

summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the ERG's summary and detailed critique in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in Tables 1.7 to 1.15.

Table 1.7: Key issue 6 Model structure - the use of a PSM, without a STM approach to verify the results

Report section	Section 4.2.2
Description of issue and why the ERG has identified it as important	NICE TSD 19 recommended the use of state transition models (STMs) alongside partitioned survival models (PSMs) to verify the plausibility of PSMs extrapolations and explore key clinical uncertainties in the extrapolation period.
What alternative approach has the ERG suggested?	To develop a STM.
What is the expected effect on the cost effectiveness estimates?	Expected impact is unclear but might be substantial given the large proportion of outcomes that are accumulated beyond the observed data.
What additional evidence or analyses might help to resolve this key issue?	Develop a STM to validate the PSM results.

Table 1.8: Key issue 7 Population – no subgroup cost effectiveness analyses presented

Report section	Section 4.2.3
Description of issue and why the ERG has identified it as important	The company did not present subgroup cost effectiveness analyses despite relevant subgroups being listed in the scope, such as histologic subtype (epithelioid, sarcomatoid, biphasic) and level of PD-L1 expression. Cost effectiveness may differ in these subgroups.
What alternative approach has the ERG suggested?	Provide subgroup cost effectiveness analyses for subgroups in the scope.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The presentation of those subgroup analyses.

Table 1.9: Key issue 8 Intervention and comparators – two-year stopping rule may not be completely adhered to in trial

Report section	Section 4.2.4
Description of issue and why the ERG has identified it as important	[redacted] continued treatment with nivolumab + ipilimumab beyond 24 months, despite the protocol stipulating a 24-months stopping rule.

Report section	Section 4.2.4
What alternative approach has the ERG suggested?	If the proportion of patients continuing nivolumab + ipilimumab beyond 24 months increases or it is deemed unlikely to be adhered to in clinical practice: scenario analyses without the stopping rule in place.
What is the expected effect on the cost effectiveness estimates?	Unclear - may increase the ICER, but effectiveness may also change.
What additional evidence or analyses might help to resolve this key issue?	Provide proportions of patients continuing treatment with nivolumab + ipilimumab beyond 24 months and duration of continued treatment in future data cuts and analyses.

Table 1.10: Key issue 9 Treatment effectiveness and extrapolation – immaturity of the long-term PFS and OS data

Report section	Section 4.2.6
Description of issue and why the ERG has identified it as important	The majority of (PF)LY were accumulated beyond the observed data period (see section 5.1) and the validation of long-term PFS and OS using external data is limited, most importantly for nivolumab + ipilimumab. Moreover, the plausibility of assuming a continued treatment effect over the lifetime horizon of the model is unclear.
What alternative approach has the ERG suggested?	Alternative approaches to estimate PFS and OS as well as assumptions related to treatment waning are considered by the ERG. However, due to the immaturity of the data, using the April 2020 database lock of CheckMate-743 (minimum follow-up for all patients was 22.1 months; 23% and 15% of patients treated with nivolumab + ipilimumab and PDC, respectively were still alive at this point), it is unclear what approach is most plausible.
What is the expected effect on the cost effectiveness estimates?	Depending on the scenario, the impact can be substantial. This is also illustrated by the large majority of (PF)LY gains that are accumulated beyond the observed data period.
What additional evidence or analyses might help to resolve this key issue?	Using CheckMate-743 data with additional follow-up data.

Table 1.11: Key issue 10 Health-related quality of life – duration of utility benefits for nivolumab + ipilimumab

Report section	Section 4.2.8
Description of issue and why the ERG has identified it as important	The treatment dependent utilities, used in the CS base-case, result in utility benefits for nivolumab + ipilimumab compared to PDC. This is 0.004 and 0.072 for the PF and PD health states. In the CS base-case, these utility benefits are maintained for the whole duration of the time horizon. The plausibility of this assumption can be debated. Although the company's responses to clarification question B12 were informative and seemed to indicate that there might be a utility benefit when patients are off treatment (clarification response Tables 26 and 27), the duration/extrapolation of the utility benefit is unclear.

Report section	Section 4.2.8
What alternative approach has the ERG suggested?	Not assuming that the utility benefits are maintained for the whole duration of the time horizon.
What is the expected effect on the cost effectiveness estimates?	The ERG adjustment using the treatment dependent utilities (with the nivolumab + ipilimumab utility benefit) up to three years and treatment independent utilities afterwards increased the ICER by ~£2,700 (when applied to the company's corrected base-case).
What additional evidence or analyses might help to resolve this key issue?	It might be informative for the company to explore the time point until which the utility benefits are maintained in CheckMate-743.

Table 1.12: Key issue 11 Resources and costs – estimation of time to treatment discontinuation

Report section	Section 4.2.9
Description of issue and why the ERG has identified it as important	Using number of mean doses to estimate time on treatment in the model may be biased due to right-censoring. Treatment cost is a major driver of cost effectiveness in this model.
What alternative approach has the ERG suggested?	Use parametric survival analysis based on TTD data from CheckMate-743: differential distributions could be used (e.g. the best-fitting generalised gamma for the nivolumab + ipilimumab arm and Gompertz for the pemetrexed + cisplatin arm as reported in Appendix K). The stopping rule for nivolumab + ipilimumab can be included by discontinuing all patients still on treatment at 24 months. Missed and delayed doses can be reflected for both arms using dose intensity as informed by CheckMate-743. No stopping rule will then be required for the pemetrexed + cisplatin arm.
What is the expected effect on the cost effectiveness estimates?	This will likely increase the ICER. The magnitude of the effect is unknown as this is depending on dose intensity.
What additional evidence or analyses might help to resolve this key issue?	Nothing further.

Table 1.13: Key issue 12 Resources and costs – uncertainty about subsequent treatments

Report section	Section 4.2.9
Description of issue and why the ERG has identified it as important	Uncertainty about proportion of patients using subsequent treatments, the mix of treatments used and the duration of subsequent treatments.
What alternative approach has the ERG suggested?	Enable in the model differential treatment durations for each treatment arm to enable further scenario analysis.
What is the expected effect on the cost effectiveness estimates?	This may increase the ICER if there is evidence for longer subsequent treatment duration in the nivolumab + ipilimumab arm than in the PDC arm, but this is currently unclear. The impact is likely small.
What additional evidence or analyses might help to resolve this key issue?	Provide CheckMate-743 analyses of subsequent treatment proportions of use, mix of treatments and duration of subsequent treatment if possible. Explore Waterhouse et al data for differential second-line treatment duration by first-line treatment (if available). Explore expert

Report section	Section 4.2.9
	opinion on subsequent treatment proportions of use, mix of treatments and duration of subsequent treatments.

Table 1.14: Key issue 13 Resources and costs – adverse events

Report section	Section 4.2.7 and Section 4.2.9
Description of issue and why the ERG has identified it as important	The exclusion of many adverse events from the model may introduce bias in favour of nivolumab + ipilimumab.
What alternative approach has the ERG suggested?	Provide cost effectiveness analyses with all-causality (treatment-emergent) adverse events instead of only treatment-related adverse events and change the restriction on the incidence to >1% instead of >2%.
What is the expected effect on the cost effectiveness estimates?	ICER will likely increase, but the impact is likely not large.
What additional evidence or analyses might help to resolve this key issue?	Provide Supplementary Table S.6.6.2 of the CheckMate-743 CSR.

Table 1.15: Key issue 14 Company's cost effectiveness results – proportion of (PF)LY accumulated beyond the observed data

Report section	Section 5.1
Description of issue and why the ERG has identified it as important	The proportion of (PF)LY accumulated beyond the observed data is substantially larger for nivolumab + ipilimumab than for PDC. Moreover, considering the increments, approximately [redacted] of the LYs are gained beyond the observed data period for nivolumab + ipilimumab compared with PDC while this is even larger (approximately [redacted] for PFLY. While the company's response to clarification questions B5 and B8 give some indication about the plausibility of the long-term extrapolations, the finding that the large majority of gains are accumulated beyond the observed data period and hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted (as requested but not provided in the company's response to clarification question B17). This includes verifying the plausibility of the partitioned survival model extrapolations.
What alternative approach has the ERG suggested?	Providing additional explanation of the mechanism by which the model generated the differences as well as a justification for why they are plausible based upon available evidence is warranted. This includes verifying the plausibility of the partitioned survival model extrapolations.
What is the expected effect on the cost effectiveness estimates?	The expected impact is unclear but is potentially substantial.
What additional evidence or analyses	See suggestions above, as well as using CheckMate-743 data with additional follow-up data.

Report section	Section 5.1
might help to resolve this key issue?	

1.6 Other key issues: summary of the ERG's view

There are no other key issues.

1.7 Summary of the ERG's view

The estimated ERG base-case ICER (probabilistic), based on the ERG preferred assumptions highlighted in Section 6.1, was £111,898 per QALY gained. The probabilistic ERG base-case analyses indicated cost effectiveness probabilities of 0%, 0% and 0% at willingness to pay thresholds of £20,000, £30,000 and £50,000 per QALY gained. The most influential adjustments were implementing treatment waning from five years onwards and using the log-logistic distribution for estimating OS in the PDC arm. The ICER increased most in the scenario analysis using TTD estimates with 100% dose intensity instead of the number of mean doses approach. Since dose intensity was likely lower in the trial, this may be regarded as a the upper bound of the ICER using alternative scenarios on time on treatment.

There is large remaining uncertainty about the effectiveness and relative effectiveness of nivolumab + ipilimumab versus PDC, which can be at least partly resolved with future analyses of CheckMate-743 data. In view of the immaturity of the CheckMate-743 study it was not possible for the ERG to quantify all uncertainty now. Further data cuts could potentially result in additional survival gains for the nivolumab + ipilimumab arm. However, it is currently questionable whether nivolumab + ipilimumab can be cost effective compared to PDC.

Table 1.16: Summary of ERG's preferred assumptions and ICER

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's corrected base-case			
Nivolumab + ipilimumab vs Pemetrexed + cisplatin or carboplatin	54,417	0.702	77,531
Matter of judgement 1: do not use piecewise approach (key issue 9)			
Nivolumab + ipilimumab vs Pemetrexed + cisplatin or carboplatin	54,579	0.719	75,867
Matter of judgement 2: use log-logistic distributions for OS in both treatment arms (using piecewise) (key issue 9)			
Nivolumab + ipilimumab vs Pemetrexed + cisplatin or carboplatin	53,269	0.576	92,413
Matter of judgement 3: implement treatment waning from 5 years onwards (key issue 9)			
Nivolumab + ipilimumab vs Pemetrexed + cisplatin or carboplatin	52,988	0.443	119,543
Matter of judgement 4: change to treatment-independent utilities from 3 years onwards (key issue 10)			
Nivolumab + ipilimumab vs Pemetrexed + cisplatin or carboplatin	54,417	0.678	80,206
ERG base-case (Changes 1-4)			

Nivolumab + ipilimumab vs Pemetrexed + cisplatin or carboplatin	53,327	0.476	112,005
ERG base-case probabilistic (5,000 runs)			
Nivolumab + ipilimumab vs Pemetrexed + cisplatin or carboplatin	53,076	0.612	111,898

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with untreated unresectable MPM.	As per scope.	Not applicable.	The inclusion criteria reported for CheckMate-743 (Table 7 of the CS) specify patients with ECOG PS 0-1. The company also did not provide comparison with BSC on the basis that BSC would only be indicated if PS>1.
Intervention	Nivolumab with ipilimumab.	As per scope.	Not applicable	The intervention is in line with the NICE scope, although dosing in CheckMate-743 was by weight. This is different to the cost effectiveness analysis, which employed a flat dosage of 360 mg every 3 weeks and was stated to align with the anticipated EMA licence.
Comparator(s)	Pemetrexed with cisplatin Raltitrexed with cisplatin (for people for whom treatment with pemetrexed is unsuitable) Pemetrexed with carboplatin (for people for whom treatment with cisplatin is unsuitable)	Pemetrexed with cisplatin or carboplatin (referred to as PDC)	In CheckMate-743, participants were randomised 1:1 to either open-label nivolumab + ipilimumab or pemetrexed + cisplatin or carboplatin. The choice of cisplatin or carboplatin was the investigator's choice, and the use of cisplatin was preferred; however, carboplatin was used at the	The choice of cisplatin or carboplatin may indicate clinically identifiable subgroups and the applicability to the English NHS of the choice of carboplatin or cisplatin as

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	Best supportive care		discretion of the investigator, and switching from cisplatin to carboplatin and vice versa were allowed if reported in the case report form. Raltitrexed is not approved for use in the UK for the first-line treatment of MPM and is not used in the NHS according to UK registry data (see Section B.1.3.4.1), as well as the UK clinical experts we have consulted (Appendix N) and the scope consultation comments from the British Thoracic Oncology Group. For these reasons, BMS have not included raltitrexed as a comparator in this submission. Best supportive care is also not included as a comparator in this submission. This is because first-line systematic anticancer therapies are only used in patients with good PS (0-1), in accordance with BTS guidelines. In line with clinical practice and the NICE recommendation for pemetrexed, the eligibility criteria of CheckMate-743 only included patients with an ECOG PS of 0-1. According to the UK clinical experts we have consulted (Appendix N) and the scope consultation comments from the British Thoracic Oncology Group, best supportive care is not an appropriate	observed in CheckMate-743 is questionable. It is unclear the extent to which raltitrexed is part of current standard of care. If the population is broader than ECOG PS 0-1, BSC should also be considered as a comparator.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			comparator because this technology relates to a particular group of fit patients for whom best supportive care would not be deemed acceptable or ethical unless specifically requested by the patient.	
Outcomes	Overall survival Progression-free survival Response rate Adverse effects of treatment Health-related quality of life	As per the scope	Not applicable	The outcomes reported are in line with the NICE scope.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	This was not included in Table 1 of the CS.	Not applicable.	The economic analysis is in line with the NICE reference case.
Subgroups to be considered	Histologic subtype (epithelioid, sarcomatoid, biphasic)	Histology: epithelioid and non-epithelioid	Clinical efficacy data are presented for the prespecified subgroup analyses in CheckMate-743, which included	Response was not reported by histological subtype and no statistical test of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	Level of PD-L1 expression	PD-L1 expression: ≥ 1% or < 1%	histology and PD-L1 expression subgroups as per the scope.	difference was reported by PD-L1 expression. No cost effectiveness analyses were presented for the subgroups.
Special considerations including issues related to equity or equality	None	The company are not aware of specific equality issues for this appraisal. However, MPM is a preventable, occupational-related disease caused by asbestos exposure. BMS wish to highlight that MPM incidence rates vary across England, with higher rates in areas of heavy industry (e.g. the northeast and southern England). Also, as MPM is a rare cancer, patients may be referred in the NHS to a limited number of specialist mesothelioma multidisciplinary teams, which may require patients to travel long distances from their homes for appointments if they live in a rural setting. Patients with MPM are often older and diagnosed at a late stage of the disease. Consequently, they can be too frail to travel for treatment, which may limit their treatment options.		No comment.

Based on Table 1 of the CS.[2]

BMS = Bristol-Myers Squibb; CS = company submission; BTS = British Thoracic Society; ECOG = Eastern Cooperative Oncology Group; MPM = malignant pleural mesothelioma; NHS = National Health Service; PD-L1 = programmed death-ligand 1; PS = performance status; QALY = quality-adjusted life year; UK = United Kingdom.

2.1 Population

The decision problem specified in the scope defines the population as adults with untreated, unresectable malignant pleural mesothelioma (MPM). The inclusion criteria reported for CheckMate-743 (Table 7 of the company submission (CS)) specify patients with ECOG PS 0-1. The company have also not provided a comparison with BSC, as argued in Table 1, because *"...first-line systematic anticancer therapies are only used in patients with good PS (0-1), in accordance with BTS guidelines."*[2]

A marketing authorisation application has been filed in Europe for nivolumab in combination with ipilimumab for the first-line treatment of adult patients with unresectable MPM. Regulatory approval and marketing authorisation are expected in [redacted].[2]

ERG comment: On the one hand, the company state that the decision problem population is as per scope and no further qualification is mentioned in the request for marketing authorisation. On the other hand, ECOG PS 0-1 is an entry criterion for the pivotal trial and the reason for excluding BSC as comparator. The ERG therefore requested clarification.[3] The company confirmed that evidence presented in the submission was only for patients with ECOG PS 0-1.[4] They did mention that many patients might have unrecorded ECOG PS, but the ERG would argue that this does not imply that status would be unknowable to the treating clinician.

2.2 Intervention

The intervention is nivolumab with ipilimumab, as per scope. It is expected to be given by intravenous infusion of 360 mg nivolumab every three weeks + 1 mg/kg ipilimumab every six weeks.[2] A 2-year treatment stopping rule is expected to be applied in clinical practice to the nivolumab + ipilimumab regimen, which is consistent with the CheckMate-743 clinical trial design.[2]

ERG comment: Nivolumab dosing in the trial was according to weight, but the cost effectiveness analysis employed a flat nivolumab dosage of 360 mg every three weeks, which was stated to align with the anticipated licence. The ERG therefore requested evidence that this difference in dosing will have no effect on effectiveness, quality of life or safety.[3] The company cited a conference presentation the purpose of which was to show that the fixed licensed dose would produce both efficacy and safety outcomes that were similar to those observed with weight-based dosing in the trial.[4] However, the pharmacokinetic analysis showed that a large difference was observed with Cmax1 peak serum concentration after the first dose, i.e. 67.4% higher with 360 mg Q3W.[5] This was reported to not be a problem because it was *"~82% below the median Cmaxss (peak serum concentration at steady state) when administered as NIVO 10 mg/kg Q2W, a dosing regimen previously demonstrated to be safe and well tolerated*". Although this does provide some reassurance regarding safety, a judgment of safety/tolerance is not a substitute for actual AE rates at the given fixed dose. The presentation also stated that: *"...efficacy and safety were evaluated by characterising the relationships between simulations of NIVO exposure and OS or grade ≥ 2 immune-mediated adverse events (grade 2+ IMAEs), respectively, using the multivariate Cox proportional-hazard model"*. However, it is not clear to the ERG precisely how outcomes could be estimated for a fixed dose without evidence from patients who received that dosing regimen. Subgroup analyses by weight were also provided, but again these do not show the effect of patients receiving a lower or higher dose, as would have been the case if dosing had been weight-based. Therefore, uncertainty remains regarding the effectiveness and safety of the expected licensed dose of nivolumab. The potential implications of this are discussed further in Section 4.2.4 and form the basis of Key Issue 8.

Despite the company stating that a 2-year stopping rule had been applied in the CheckMate-743 trial, Figure 10 in Appendix K appears to show two patients still on treatment at 25 months.[6]

2.3 Comparators

The NICE scope listed the following four comparators:

- Pemetrexed with cisplatin
- Raltitrexed with cisplatin (for people for whom treatment with pemetrexed is unsuitable)
- Pemetrexed with carboplatin (for people for whom treatment with cisplatin is unsuitable)
- Best supportive care

The company only included one comparator, which was a combination of pemetrexed plus either cisplatin or carboplatin, referred to as PDC, i.e. they chose not to separate into two comparators on the basis that which one was received in CheckMate-743 was according to investigator choice (IC). The clinical study report (CSR) states*: "The use of cisplatin was preferred; however, carboplatin may be used at the discretion of the investigator."*[7]

ERG comment: The British Thoracic Society (BTS) guideline recommends carboplatin only*: "Where cisplatin is contraindicated, or has adverse risk,"* (p.i2).[8] This might imply clinically identifiable subgroups and thus that the most appropriate way of estimating the effectiveness and cost effectiveness would be by such subgroups. However, the ERG recognises that such analyses may not be required if the choice of comparator in CheckMate-743 was made in a way that is consistent with English NHS practice and that the proportion of those that would receive each treatment is approximately that which would be observed in the English NHS. The ERG also acknowledges that subgroup analysis by cisplatin or carboplatin would be hindered by the fact that the choice of cisplatin or carboplatin was at the discretion of the clinician and not part of the randomisation. Therefore, the intention to treat (ITT) analysis of the control group as a whole is the most appropriate one. The ERG therefore asked for reassurance of the applicability of CheckMate-743 to English NHS practice to which the company responded by providing a set of estimates of the percentages of United Kingdom (UK) patients treated with either carboplatin or cisplatin.[4] Although the company seemed to believe that these estimates validated the results of CheckMate-743, the percentage of patients who had received carboplatin or cisplatin varied between sources:

- UK National Mesothelioma Audit 2020: of patients treated with chemotherapy, pemetrexed with carboplatin was the most common regimen used (48%), followed by pemetrexed with cisplatin (20%), i.e. about 42% of those who received PDC[9].
- Real-world treatment data from the CAS registry in England from January 2013-December 2017 (3,159 unresected patients received first-line SACT): of patients treated with PDC, [redacted].[1]
- EU cross-sectional study including a smaller cohort of 248 UK patients: of patients treated with PDC, [redacted].[10]

Therefore, a key issue remains given the continued uncertainty regarding the applicability of the comparator used in CheckMate-743.

As stated in Section 2.1, the ERG also requested clarification on the applicability of BSC as comparator.[3] The company responded, as described in Section 2.1, that the index population of the evidence submission is those with ECOG PS 0-1, which would seem to eliminate BSC as a comparator.[4]

In support of the omission of raltitrexed as a comparator, the CS stated that: *"The BTS guidelines state that pemetrexed can be replaced with raltitrexed and cisplatin can be replaced with carboplatin as alternatives; however, in clinical practice, raltitrexed is not used in the UK NHS."* The main reference given for treatment patterns is the 2016-2018 UK National Mesothelioma Audit; this report does not describe the chemotherapy regimens received by patients who did not receive pemetrexed with carboplatin or cisplatin (32%) and does not mention raltitrexed.[9] The company did provide expert opinion in Appendix N that raltitrexed is not used, but this is only from two clinicians.[6] The ERG therefore requested that the company either provide further evidence that raltitrexed is not currently used in the UK NHS or include raltitrexed as a comparator.[3] The company responded by providing two sources of data:[4]

- Real-world treatment data from the CAS registry in England from January 2013-December 2017: no recorded use of raltitrexed during the study period.[1]
- Real-world cross-sectional study on treatment patterns in Europe. In the UK in 2019, [redacted] received combination treatment with off-label raltitrexed.[10]

The ERG is therefore satisfied that raltitrexed can reasonably be omitted as a comparator.

2.4 Outcomes

The outcomes are as per scope:[2]

- OS
- PFS
- Response rate
- Adverse effects of treatment

2.5 Other relevant factors

There are none.

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

A clinical systematic literature review (SLR) was performed in October 2020 according to NICE requirements to identify studies relevant to nivolumab + ipilimumab for the treatment of previously untreated unresectable MPM in adults.[2]

3.1.1 Searches

Appendix D of Document C of the CS details a SLR conducted to identify randomised and non-randomised trials evaluating the efficacy and safety of first-line, second-line and later treatments for adults with MPM. The last search was undertaken on 5 October 2020. There were no date limits.[6] A language limit was reported but this did not appear to be applied at the searching stage. A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS and response to clarification)

	Resource	Host/source	Date ranges	Dates searched
Electronic databases	Embase	Embase.com	From inception	5.10.21
	MEDLINE	Embase.com		
	MEDLINE In-Process and Ahead of Print	PubMed		
	CENTRAL	Wiley		
	CDSR	Wiley		
Conference proceedings	American Society of Clinical Oncology (ASCO)	https://meetinglibrary.asco.org/results/(Keywords:"Mesothelioma");page=0	2018-2020	October 2020
	European Society for Medical Oncology (ESMO)	https://www.sciencedirect.com/search?qs=mesothelioma&pub=Annals%20of%20Oncology&cid=321639&years=2020&lastSelectedFacet=years	2018-2020	
	American Association for Cancer Research (AACR)	https://www.aacr.org/professionals/meetings/previous-aacr-meetings/previous-aacr-meetings-2018/	2018	
		https://www.aacr.org/professionals/meetings/previous-aacr-meetings/previous-aacr-meetings-2019/ https://cancerres.aacrjournals.org/content/79/13_Supplement	2019	
		https://www.aacr.org/professionals/meetings/previous-aacr-meetings/previous-aacr-meetings-2018/	2020	

	Resource	Host/source	Date ranges	Dates searched
	International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	https://www.ispor.org/heor-resources/presentations-database/search	2018-2020	
	World Conference on Lung Cancer (WCLC)	https://wclc2018.iaslc.org/wp-content/uploads/2018/09/WCLC2018-Abstract-Book_vF-LR-REV-SEPT-25-2018.pdf	2018	
		https://wclc2019.iaslc.org/wp-content/uploads/2019/08/WCLC2019-Abstract-Book_web-friendly.pdf	2019	
	European Lung Cancer Congress (ELCC)	https://www.jto.org/issue/S1556-0864(18)X0004-5	2018	
		https://www.sciencedirect.com/journal/annals-of-oncology/vol/30/suppl/S2?page=3#article-201	2019	
	International Mesothelioma Interest Group (IMIG)	Not searched		
Additional resources				
National Institute for Health and Care Excellence (NICE)				
Scottish Medicines Consortium (SMC)				
Institute for Quality and Efficiency in Health Care (IQWiG)				
Haute Autorité de Santé (HAS)				
Canadian Agency for Drugs and Technologies in Health (CADTH)				
Pharmaceutical Benefits Advisory Committee (PBAC)				
Food and Drug Administration (FDA)				
European Medicines Agency (EMA)				
Gesellschaft der Epidemiologischen Krebsregister in Deutschland (GEKID)				
Belgian Cancer Registry				
Dutch Cancer Registry				
Italian Association of Cancer Registries (ITACAN)				
Red Española de Registros de Cáncer (REDECAN)				
Nordic Cancer Registry (NORDCAN)				
Surveillance, Epidemiology, and End Results Program (SEER)				
National Lung Cancer Audit annual report				

ERG comment:

- A range of databases and conference proceedings were searched as well as health technology assessment (HTA) agencies, regulatory agencies and registries. The CS provided sufficient details for the ERG to appraise the literature searches.
- The update searches which were reported, were well-conducted and documented making them transparent and reproducible.
- Databases were searched from inception to the search date.
- A restriction to English language publications was reported but this did not appear to be a searching restriction.
- Study design filters were appropriately used although not referenced in the CS. Upon clarification it was explained that they were based on clinical effectiveness filters from a number of sources including Scottish Intercollegiate Guidelines Network (SIGN), British Medical Journal (BMJ) Best Practice and Canadian Agency for Drugs and Technologies in Health (CADTH). They appeared sufficient to find both randomised and non-randomised study designs.
- Cochrane Library searches for observational studies and real-world evidence reported use of a filter and the use of filters is not recommended in Cochrane Library databases which are study design specific.[11] However, as the results for the Cochrane Library observational studies search had the same number of hits as the Cochrane Library search for controlled evidence and the flowchart does not combine these two searches, it is likely that the Cochrane Library search for observational studies and real-world evidence was incorrectly reported.

3.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for randomised controlled trials (RCTs) and non-RCTs is presented in Table 3.2. All inclusion screening was performed by two independent reviewers, followed by a quality check by a third independent reviewer.[6]

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Description	Justification
Inclusion criteria		
Population	Gender: Any Race: Any Ethnicity: Any Disease: Malignant pleural mesothelioma	Consistent with scope.
Interventions	Doxorubicin Picoplatin Oxaliplatin Raltitrexed Cyclophosphamide Pemetrexed Carboplatin Gemcitabine Vinorelbine Fluorouracil Vinblastine	Unclear given the decision problem excluded all but the comparator in the company trial, CheckMate-743.

	Description	Justification
Inclusion criteria		
	Pemetrexed + cisplatin or carboplatin Erlotinib Bevacizumab Cisplatin Navelbine Platinum Topotecan Liposomal doxorubicin Irinotecan Mitomycin Paclitaxel Adriamycin Nivolumab + ipilimumab Pembrolizumab Best supportive care Active symptom control	
Outcomes	Overall survival Progression-free survival Disease control rate Duration of response Post progression survival Duration of therapy Overall response rate Adverse effects Study withdrawals/discontinuations Time-to-treatment discontinuation	Reported as outcomes to extract, rather than to include.
Study design	RCT: parallel group (triple/double blind) RCT: cross-over (triple/double blind) RCT: post hoc and open-label extension RCTs: Unblinded Pooled studies of RCTs Non-randomised controlled trials Cohort studies (retrospective observational) Cohort studies (prospective observational) Single-arm studies Literature reviews/systematic reviews/meta-analysis/relevant general reviews	Unclear why non-RCTs were included given that company trial, CheckMate-743, which is an RCT, was the only one included.

	Description	Justification
Inclusion criteria		
Language restrictions	English language only	Not reported.
Exclusion criteria: None reported.		
Source: Table 1 of Appendix D.[6] RCT = randomised controlled trial		

3.1.3 Data extraction

All data extraction was performed by two independent reviewers, followed by a quality check by a third independent reviewer.[6]

3.1.4 Quality assessment

The critical appraisal of randomised studies was conducted using the NICE checklist as recommended in the NICE STA manufacturer's template.[12]

3.1.5 Evidence synthesis

Because only one RCT was included, there was no synthesis.[2]

ERG comment: The systematic review appears to have been largely well conducted with the inclusion of more studies than are required given that the submission relies solely upon evidence from the CheckMate-743 trial. This trial was considered to be the most appropriate evidence, assuming that PDC is the only relevant comparator (see Section 2.3), because it provides a direct comparison between nivolumab + ipilimumab and PDC.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Design (including statistical analyses) of CheckMate-743 trial

The CheckMate-743 trial is an international, multicentre, randomised, open-label, active-controlled phase 3 trial (See Table 3.3).[2] The population of the CheckMate-743 trial included individuals who had a histological diagnosis of MPM, had advanced unresectable disease that was not amenable to therapy, had available pathological samples for centralised programmed death-ligand 1 (PD-L1) immunohistochemistry (IHC) testing, ECOG PS 0-1, and could have had prior palliative radiotherapy.[2] The trial locations comprised of 103 sites, with six of these sites being based in the UK, however, additional locations were not further identified.[2] The intervention in the CheckMate-743 trial was nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q3W for up to two years. The comparator was cisplatin or carboplatin + pemetrexed Q3W for six cycles. The use of cisplatin or carboplatin was based on the investigator's choice and, thus, are not treated as separate comparators. Statistical analyses are shown in Table 3.4.

Table 3.3: CheckMate-743: study design

Study	CheckMate-743 (NCT02899299)
Study Design (n)	International, multicentre, randomised, open-label, active-controlled phase 3 trial (n=605)
Population	• Males and females aged ≥18 years. • Histological diagnosis of MPM; determination of epithelioid vs. non-epithelioid histology.

Study	CheckMate-743 (NCT02899299)
	• Patients with advanced unresectable disease that is not amenable to therapy with curative intent (surgery with or without chemotherapy). • Available (archival and/or fresh) pathological samples for centralised PD-L1 IHC testing. • Prior palliative radiotherapy is acceptable; however, ≥14 days must have passed prior to first treatment, and all signs of toxicity must have remitted. Prior prophylactic radiotherapy to a pleurodesis drainage tract or biopsy site is allowed. • ECOG PS 0-1. • Measurable disease is defined as: – Mesothelioma tumour thickness perpendicular to the chest wall or mediastinum that can be measured in up to 2 positions at 3 separate levels on transverse cuts of computed tomography scan (cuts must be ≥10 mm apart), for a total of up to 6 measurements. Each single tumour measurement must be ≥10 mm to qualify as measurable disease and contribute to the sum that defines the pleural measurement. – Non-pleural metastatic target lesions measured unidimensional as per RECIST v1.1 criteria. Patients who present without pleural lesions that can be considered measurable but with metastatic lesions meeting criteria for target lesion by RECIST v1.1 criteria may be considered for inclusion after consultation with the Medical Monitor. As of 3 April 2020, database lock, 713 patients enrolled included: 605 patients randomised to each treatment arm: • 303 patients in the Nivolumab + ipilimumab arm • 302 patients in the PDC arm
Intervention	Nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W for up to 2 years, n = 303
Comparator	PDC – pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin (AUC of 5 mg/mL/minute), on day 1 of a 21-day cycle for 6 cycles
Reported outcomes specified in the decision problem	Measures of disease severity and symptom control: • OS • ORR • PFS HRQoL: • EQ-5D-3L • VAS • LCSS-Meso Safety outcomes: • AEs
All other reported outcomes	• Disease control rate (DCR) • Composite correlation of PD-L1 • Time to response (TTR) • Duration of response (DOR) • Eastern Cooperative Oncology Group performance status (ECOG PS)
Duration of study and follow-up	CheckMate-743 is ongoing. At the latest database cut of 3 April 2020 after 419 observed events, the median follow up was 29.7 months. Most of the patients received around 90% or more of planned doses. The median duration of patients in the nivolumab + ipilimumab arm was longer than patients in the PDC arm.

Study	CheckMate-743 (NCT02899299)
	The maximum duration of treatment per protocol was 24 months for nivolumab + ipilimumab and 6 cycles of PDC. A final primary OS analysis will be performed when 473 deaths have occurred. Estimated date for primary completion is April 2021and study final completion date is April 2022.
Countries	103 sites in Australia, New Zealand, Europe, Asia, North America, and South America (6 sites in the UK)

Source: Adapted from Table 6 and Table 7 of the CS [2]
AE = adverse event; BICR = blinded independent central review; DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; MPM = malignant pleural mesothelioma; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks. AUC = area under the curve; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; IHC = immunohistochemistry; LCSS-Meso = Lung Cancer Symptom Scale–Mesothelioma; PD 1 = programmed death-1; PDC = platinum-based doublet chemotherapy; PD-L2 = programmed death-ligand 2; RECIST = Response Evaluation Criteria in Solid Tumours; TTR = time to response; UK = United Kingdom.

Follow-up visit 1 = 30 days from the last dose ± 7 days or coincides with the date of discontinuation (± 7 days) if date of discontinuation is > 35 days after last dose. Follow-ups visit 2 = 90 days (± 7 days) from follow-up visit 1.

Table 3.4: CheckMate-743 statistical analyses

Study	CheckMate-743 (NCT02899299)
Hypothesis objectives	Evaluate and compare the OS of nivolumab + ipilimumab vs. pemetrexed + cisplatin or carboplatin as first-line treatment in patients with unresectable MPM
Statistical analysis	OS was analysed between the treatment groups at the interim and final analyses by utilising a stratified log-rank test. Stratified factors observed were histology and sex of patients. An O'Brien and Fleming α-spending function was used to determine the nominal significance levels for the interim and final analyses. The stratified hazard ratio between the treatment groups was to be introduced along with 100*(1-α) % CI (adjusted for interim). A two-sided P value was accounted for the analysis of the OS. OS was to be assessed by utilizing KM techniques. A two-sided 95% CI for median OS in each treatment group was to be computed via the log-log transformation method. OS rates at fixed time points (e.g. six months, depending on the minimum follow-up) were to be introduced alongside their associated 95% CIs. These estimates were derived from the KM estimates and relating CIs were determined on Greenwood formula for variation derivation and on log-log transformation applied on the survivor function. The status of patients who are controlled in the OS KM investigation was arranged for every treatment groups utilising the accompanying classifications: • On study (on treatment, in follow up) • Off study (lost to follow up, withdrawn consent, never treated) The influence of baseline and demographic characteristics on the treatment effect among all randomised patients was also to be explored for specific subgroups, including age, sex, race, ECOG PS, histology, and PD-L1. • Principal analyses of PFS and ORR were based on the BICR evaluation. No formal testing of the secondary objectives was done. Results were descriptive. PFS was estimated using the KM methodology and analysed similarly to OS. Response and disease

Study	CheckMate-743 (NCT02899299)
	control rate estimates were presented along with their exact two-sided 95% CIs by Clopper and Pearson. • DOR was to be estimated using the KM product limit method. CIs for secondary endpoints were at the two-sided 95% level. • Safety: Descriptive statistics of safety were presented using MedDRA version 22.1 and NCI-CTCAE version 4.0. All on-study AEs, drug-related AEs, SAEs, drug-related SAEs, IMAEs, and select AEs were tabulated using worst grade per NCI-CTCAE version 4.0 criteria by system organ class and preferred term. Frequency, management, and resolution of IMAEs and select AEs were analysed. Patient-reported outcome analyses: Continuous data were described using descriptive statistics. Categorical data were summarised using counts and percentages, for which "missing" was used when applicable. Where relevant, significance testing was two-sided at the 0.05 level, with no adjustment for multiplicity.
Sample size, power calculation	For the OS primary endpoint, a general two-sided alpha (type 1 error rate) was set at 0.05. 605 patients were randomized with 1:1 proportion to two treatment arms. 473 OS events were required for the final analysis. The sample size was determined to compare OS between nivolumab + ipilimumab (Arm A) versus pemetrexed + cisplatin or carboplatin regime (Arm B). One conventional interim analysis was performed for OS at 403 OS events. Key parameters for the primary analysis were as per the following: • Targeted power: 90% • Target hazard ratio: 0.72 • 0-6 months: 1 • 6-34 months: 0.767 • After 34 months: 0.002 • Alpha: 0.05, two-sided (0.03 at interim; 0.041 at final analyses) • Sample size: 606 • Target number of events: 473 • Expected number of events for interim analysis: 403 (85% of target) • Duration (monthly accrual rate = 34 patients): 56 months
Date management and patient withdrawals	OS was censored on the last date a patient was known to be alive. For PFS, patients who died with no reported progression were considered to have progressed on the date of death. Patients who did not progress or die were censored on the date of their last evaluable tumour assessment. Patients who did not have any on-study tumour assessments and did not die were censored on their date of randomisation. Patients who had palliative local therapy or initiated anticancer therapy without a prior reported progression were censored on the date of their last evaluable tumour assessment on or before the initiation of subsequent anticancer therapy or palliative local therapy. For DOR, patients who did not progress or die were censored on the date of their last evaluable tumour assessment. Patients who started subsequent therapy without a prior reported progression were censored at the last evaluable tumour assessments before initiation of the subsequent anticancer therapy. Patients who died without a reported prior progression were considered to have progressed on the date of their death. For patients who neither progressed nor died, DOR was censored on the date of their last evaluable tumour assessment.

Study	CheckMate-743 (NCT02899299)
Missing data	Patients who remained lost to follow-up then the last recognised alive date was determined by an investigator was reported and accounted in the patient's clinical records.

Source: Adapted from Table 9 of the CS.[2]
AE = adverse event; BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; IMAE = immune-mediated adverse event; KM = Kaplan-Meier; MedDRA = Medical Dictionary for Regulatory Activities; MPM = malignant pleural mesothelioma; NCI-CTCAE = Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; SAE = serious adverse event.

3.2.2 Baseline characteristics of CheckMate-743 trial

The baseline characteristics of the CheckMate-743 trial are presented in Table 3.5. The participants in the trial were randomised on a 1:1 basis.[2] The median age of the randomised participants was 69.0 years. The majority of participants were white and male and at baseline had an advanced disease stage.[2] Almost all participants had quantifiable PD-L1 expression, with 77.0% at ≥1% and 23% <1%.[2] According to UK clinical experts, the trial population was representative of a treatment naïve MPM population in England.[2]

Table 3.5: CheckMate-743: baseline demographics (all randomised patients)

	Nivolumab + ipilimumab (n = 303)	PDC (n = 302)	Total (n= 605)
Age, median (IQR), years	69 (65-75)	69 (62-75)	69 (64-75)
Male, N (%)	234 (77)	233 (77)	467 (77)
ECOG performance status, N (%)			
0	114 (38)	128 (42)	242 (40)
1	189 (62)	173 (57)	362 (60)
Disease stage at study entry			
I	12 (4)	20 (7)	32 (5)
II	23 (8)	22 (7)	45 (7)
III	103 (34)	106 (35)	209 (35)
IV	160 (53)	149 (49)	309 (51)
Unknown	5 (2)	5 (2)	10 (2)
Smoking status, N (%)			
Never	127 (42)	122 (40)	249 (41)
Current/former	173 (57)	171 (57)	344 (57)
Histology,[a] N (%)			
Epithelioid	229 (76)	227 (75)	456 (75)
Non-epithelioid[b]	74 (24)	75 (25)	149 (25)
Prior radiotherapy, %	10	9	9
PD-L1 quantifiable at baseline,[c] N	289	297	586
< 1%,[d] N (%)	57 (20)	78 (26)	135 (23)
≥ 1%,[d] N (%)	232 (80)	219 (74)	451 (77)

	Nivolumab + ipilimumab (n = 303)	PDC (n = 302)	Total (n= 605)
Sources: Table 8 CS.[2] ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; IQR = interquartile range; PDC = platinum-based doublet chemotherapy; PD-L1 = programmed death-ligand 1. [a] Based on case report form source. [b] Included 47% sarcomatoid and 53% mixed/other in the nivolumab + ipilimumab arm and 48% and 52%, respectively, in the chemotherapy arm. [c] Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [d] Based on PD-L1 quantifiable at baseline, 95% and 98% of patients in the nivolumab + ipilimumab and chemotherapy arms, respectively.			

ERG comment: Baseline characteristics seemed to be similar between the arms in the trial. However, the CheckMate-743 had just 38 patients from the UK, which was 6.3% of total patients randomised. The company was therefore requested to provide evidence of generalisability to the UK in response to the clarification letter.[4] They stated that the clinicians the company consulted for this appraisal considered this evidence in addition to the baseline characteristics of the trials to indicate generalisability to English NHS practice.

3.2.3 Quality of CheckMate-743 trial

The critical appraisal of RCTs was conducted utilising the NICE checklist. The quality assessment of the CheckMate-743 trial is presented in Table 3.6. It was unclear how many reviewers were involved in the quality assessment.

Table 3.6: Quality assessment of CheckMate-743 (NCT02899299)

	Company appraisal	ERG appraisal
Was randomisation carried out appropriately?	Yes/No	Yes
Was the concealment of treatment allocation adequate?	No – open-label trial	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No – open-label trial	No
Were there any unexpected imbalances in dropouts between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No

	Company appraisal	ERG appraisal
Was randomisation carried out appropriately?	Yes/No	Yes
Did the analysis include an ITT analysis? **If so, was this appropriate and were appropriate methods used to account for missing data?**	Yes	Yes
Did the authors of the study publication declare any conflicts of interest?	Yes	Yes
Does the trial reflect routine clinical practice in England?	Yes	Unsure
Sources: Table 12, CS.[2] ITT = intention to treat.		

ERG comment: The ERG agrees with the quality assessment. The CheckMate-743 trial was a high-quality study in some respects, the major flaw being in the lack of blinding and questionable applicability to clinical practice in the NHS in England given the small number of UK patients and possible variation in judgement as to whether carboplatin or cisplatin prescribed (see also Section 2.3).

3.2.4 Results of CheckMate-743 trial

The results presented in the CS were reported to be from an interim analysis with a database lock of 3 April 2020.

3.2.4.1 Overall survival

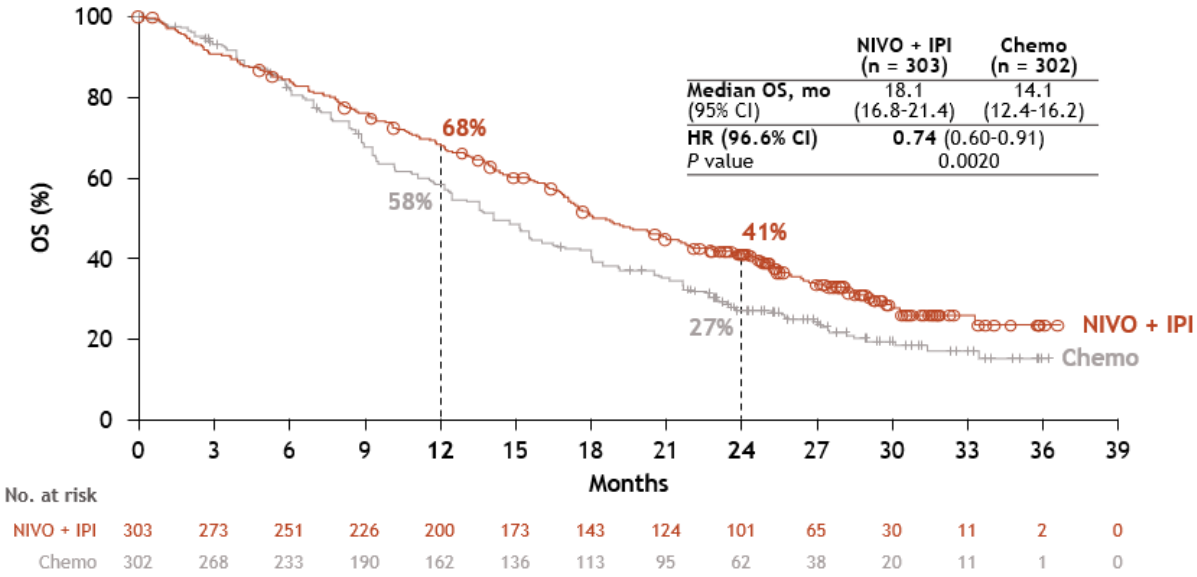
OS was the primary endpoint of the CheckMate-743 trial and was defined at the time of randomisation to the date of death from any cause. According to the CS, a statistically significant benefit was observed for patients who were treated with nivolumab + ipilimumab when compared to patients treated with PDC.[2] The company noted that treatment with nivolumab + ipilimumab reduced the risk of death by 26% when compared to PDC (hazard ratio (HR), 0.74; 96.6% confidence interval (CI), 0.60 to 0.91; stratified log-rank $P = 0.0020$).[2] Those treated with nivolumab + ipilimumab were noted to have a median OS of 18.1 months (95% CI: 16.8 to 21.4 months), whereas the those treated with PDC had a median OS of 14.1 months (95% CI: 12.4 to 16.2 months). The OS rates for all randomised patients are depicted below in Table 3.7. The company notes that additional follow-up will demonstrate a long-term, durable benefit with dual immunotherapy with nivolumab + ipilimumab.[2]

The ERG requested results of formal statistical analyses for the comparison of the OS-related outcomes, as presented in Table 3.7, to which the company responded that OS was compared in two randomised arms via a two-sided, long-rank test stratified by histology and gender at the interim analysis cut-off only.[4] In the response to clarification, the company also noted that at the time of the prespecified interim analysis, the median follow-up for OS 29.7 months (interquartile range (IQR): 26.7 to 32.9), with a minimum of follow-up of 22.1 months.[4]

Table 3.7: CheckMate-743: overall survival rates – all randomised patients

Median overall survival (95% CI)	Nivolumab + ipilimumab (n=303)	PDC (n=302)
6 months	84.0 (79.4-87.7)	82.2 (77.3-86.2)
12 months	67.9 (62.3-72.8)	57.7 (51.7-63.2)
18 months	50.5 (44.7-56.1)	40.6 (34.8-46.3)
24 months	40.8 (35.1-46.5)	27.0 (21.9-32.4)
Sources: Table 14, CS[2] CI= confidence interval; PDC= platinum-based doublet chemotherapy. Note: Based on Kaplan-Meier estimates.		

Figure 3.1: CheckMate-743: Kaplan-Meier plot of overall survival (all randomised patients)

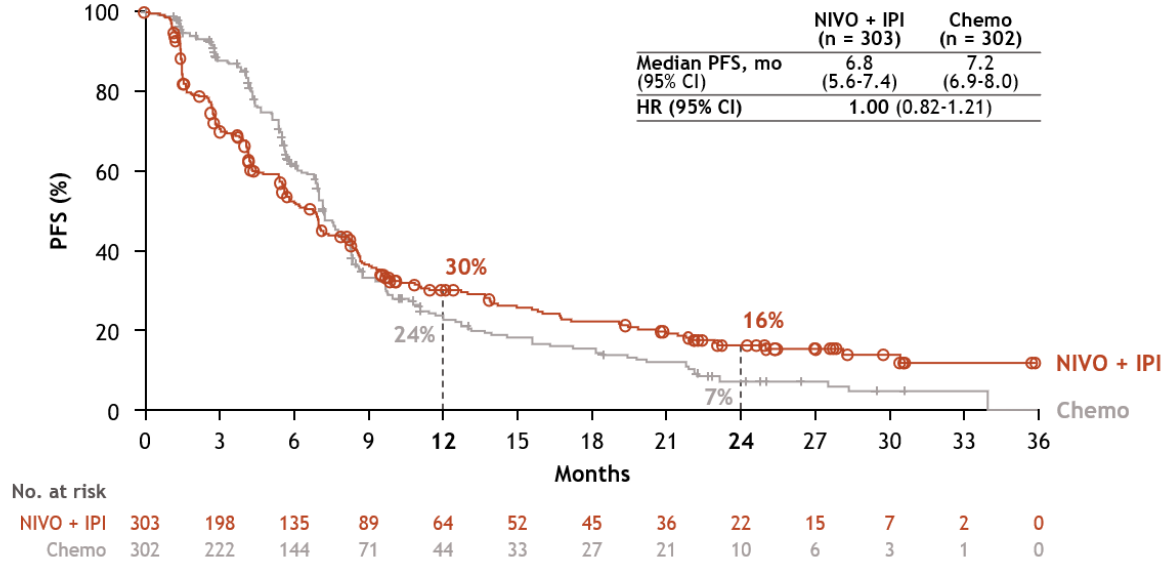


CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival.
Notes: Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm and 41% in the chemo arm; subsequent immunotherapy was received by 3% and 20%, and subsequent chemotherapy by 43% and 32%, respectively.
Chemo in figure refers to platinum-based doublet chemotherapy.
Source: Figure 12 from the CS.[2]

3.2.4.2 Progression-free survival

At the point of the interim analysis, 85.1% of patients in both arms had experienced a progression event according to the BICR assessment.[2] However, there was no statistically significant difference in PFS between patients treated with nivolumab + ipilimumab and patients treated with PDC.[2] The median PFS for patients treated with nivolumab + ipilimumab was 6.8 months (95% CI: 5.6 to 7.4 months), whereas the median PFS in the PDC group was 7.2 months (95% CI: 6.9 to 8.0 months).[2]

Figure 3.2: CheckMate-743: Kaplan-Meier plot of progression-free survival by blinded independent central review (all randomised patients)



CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PFS = progression-free survival.
Notes: Per adapted mRECIST for pleural mesothelioma lesions and/or RECIST v1.1 for non-pleural lesions.
Chemo in figure refers to platinum-based doublet chemotherapy.
Source: Baas [13] Based on Figure 13 of the CS [2]

3.2.4.3 Objective response

In the CheckMate-743 trial, the nivolumab + ipilimumab and PDC arms displayed similar objective response rate (ORR) according to the BICR.[2] Patients in the nivolumab + ipilimumab arm had an ORR per BICR of 39.6% (95% CI: 34.1to 45.4%), whereas those in the PDC arm had an ORR of 42.7% (95% CI: 37.1 to 48.5%).[2] The company noted that a BOR of CR was observed in 5 (1.7%) patients in the nivolumab + ipilimumab group, while this was not observed in any patients in the PDC arm.[2]

ORR per BICR was noted to be similar in both treatment arms in patients with PD-L1-positive tumours.[2] When the ERG requested further clarification regarding the use of any formal statistical analyses for the comparison of all response outcomes, the company reiterated that results were descriptive.[4] In the response to clarification, the company provided additional analyses of the response outcomes with 95% CIs presented in Table 3.8.

Table 3.8: Response rate per BICR

Outcome	Nivolumab + ipilimumab (n=303)	PDC (n=302)
ORR per BICR[a]		
ORR,[b] n (% [95% CI])	120/303 39.6 (34.1-45.4)	129/302 42.7 (37.1-48.5)
Median TTR, months	2.7	2.5
DOR (95% CI), months[c]	11.0 (8.1-16.5)	6.7 (5.3-7.1)
Best overall response (BOR), n (% [95% CI])		

Outcome	Nivolumab + ipilimumab (n=303)	PDC (n=302)
CR	5/303 (1.7 [0.5-3.8])	0 (0)
PR	115/303 38.0 (32.5-43.7)	129/302 42.7 (37.1-48.5)
Stable disease	112/303 37.0 (31.5-42.7)	125/302 41.4 (35.8-47.2)
Progressive disease	55/303 18.2 (14.0-23.0)	14/302 4.6 (2.6-7.7)
DCR (95% CI), % (CR+PR+SD)	76.6 (71.4-81.2)	85.1 (80.6-88.9)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; HR = hazard ratio; ORR = objective response rate; OS = overall survival; PDC = platinum-based doublet chemotherapy; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; TTR = time to response.

[a] Per adapted modified RECIST for pleural mesothelioma lesions and/or RECIST v1.1 for non-pleural lesions.

[b] 95% CI Clopper and Pearson Method.

[c] Kaplan-Meier estimates.

Source: Table 7 in the response to clarification.[4]

ERG comment: At the time of the interim analysis with a database lock of 3 April 2020, a statistically significant OS benefit was observed for patients who were treated with nivolumab + ipilimumab when compared to patients treated with PDC.[2] However, there was no statistically significant difference in PFS and results for ORR were similar.[2] The ERG did request results from a more recent data cut, but the company replied: "*As CheckMate-743 met its primary endpoint at the 3 April 2020 database lock, this analysis was considered the final analysis. However, follow up of CM-743 is ongoing and additional data cuts are expected, likely in Q2/Q3 2021 (TBC). As the timing of the analysis is event driven, there is uncertainty on the exact timing of future database locks*."[4] Although it is unlikely that the results will change the interpretation that nivolumab + ipilimumab is more effective in terms of OS, the precise size of the difference might be important particularly in determining if cost effective. The interpretation of PFS may change, given that progression data are incomplete.

3.2.4.4 Adverse events

The CS noted that the frequencies of all-cause AEs and treatment-related adverse events (TRAEs) were similar between treatment groups (see Table 3.9).[2]

Table 3.9: CheckMate-743: safety summary – all treated patients

Safety parameters, n (%)	Nivolumab + ipilimumab (n=300)		PDC (n=284)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
All-causality SAEs	164 (54.7)	103 (34.3)	72 (25.4)	54 (19.0)
Treatment-related SAEs	64 (21.3)	46 (15.3)	22 (7.7)	17 (6.0)
All-causality AEs leading to discontinuation	88 (29.3)	59 (19.7)	58 (20.4)	28 (9.9)

Safety parameters, n (%)	Nivolumab + ipilimumab (n=300)		PDC (n=284)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Treatment-related AEs leading to discontinuation	69 (23.0)	45 (15.0)	45 (15.8)	21 (7.4)
All-causality AEs	299 (99.7)	159 (53.0)	277 (97.5)	121 (42.6)
Treatment-related AEs	240 (80.0)	91 (30.3)	233 (82.0)	91 (32.0)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PDC = platinum-based doublet chemotherapy; SAE = severe adverse event.
Note: Definitions of events were based on MedDRA version 22.1; Common Terminology Criteria version 4.0. Includes events reported between first dose and 30 days after the last dose of study drug, unless otherwise indicated.
Source: Table 17 of the CS [2]

The most commonly reported TRAEs with nivolumab + ipilimumab were diarrhoea and pruritus.[2] For patients who were treated with PDC, the most commonly experienced TRAEs were nausea, anaemia, and neutropenia, as presented in Table 3.10.[2] The company noted that most of the treatment-related select AEs and most IMAEs had resolved at the time of the database lock, with the exception of endocrine-related events.[2] The reported median time to resolution ranged from 0.14 to 12.14 weeks for select AEs and 0.14 to 17.14 weeks for IMAEs.[2]

Table 3.10: CheckMate-743: treatment-related adverse events – all treated patients

Safety parameters, n (%)	Nivolumab + ipilimumab[a] (n=300)		PDC[b] (n=284)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
TRAEs leading to discontinuation of any component of the regimen[c]	69 (23.0)	45 (15.0)	45 (15.8)	21 (7.4)
Serious TRAEs[c]	64 (21.3)	46 (15.3)	22 (7.7)	17 (6.0)
Any TRAE[c]	240 (80.0)	91 (30.3)	233 (82.0)	91 (32.0)
≥ 15% of patients in any treatment group				
Diarrhoea	62 (20.7)	10 (3.3)	21 (7.4)	2 (0.7)
Pruritus	49 (16.3)	3 (1.0)	1 (0.4)	0
Fatigue	41 (13.7)	3 (1.0)	55 (19.4)	5 (1.8)
Nausea	30 (10.0)	1 (0.3)	104 (36.6)	7 (2.5)
Decreased appetite	29 (9.7)	2 (0.7)	50 (17.6)	2 (0.7)
Asthenia	25 (8.3)	0	44 (15.5)	12 (4.2)
Anaemia	6 (2.0)	1 (0.3)	102 (35.9)	32 (11.3)
Neutropenia	2 (0.7)	2 (0.7)	71 (25.0)	43 (15.1)
Treatment-related select AEs				
Endocrine	52 (17.3)	4 (1.3)	0	0
Gastrointestinal	66 (22.0)	16 (5.3)	23 (8.1)	3 (1.1)
Hepatic	36 (12.0)	16 (5.3)	6 (2.1)	0
Pulmonary	20 (6.7)	2 (0.7)	0	0
Renal	15 (5.0)	4 (1.3)	19 (6.7)	1 (0.4)

Safety parameters, n (%)	Nivolumab + ipilimumab[a] (n=300)		PDC[b] (n=284)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Skin	108 (36.0)	9 (3.0)	28 (9.9)	1 (0.4)
Hypersensitivity/infusion reactions	36 (12.0)	4 (1.3)	7 (2.5)	0

AE = adverse event; PDC = platinum-based doublet chemotherapy; TRAE = treatment-related adverse event.
Note: Person-years of exposure: nivolumab + ipilimumab, 220.3; chemotherapy, 94.5. Nivolumab + ipilimumab dosages were nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks.
[a] Median (interquartile range) doses for treated patients: nivolumab, 12.0 (5.0-23.5); ipilimumab, 4.0 (2.0-7.0).
[b] Median (interquartile range) doses for treated patients: pemetrexed, 6.0 (4.0-6.0); cisplatin 5.0 (3.0-6.0); carboplatin 6.0 (4.0-6.0).
[c] Includes events reported between first dose and 30 days after last dose of study drug.
Source: Table 18 of the CS[2]

In the request to clarification, the company also provided a table reporting treatment emergent i.e. all-cause AEs of grade 3 or 4 severity (≥1%).[4] This is shown in Table 3.11.

Table 3.11: All-cause adverse events of grade 3 or 4 severity (≥1%)

Event, n (%)	Nivolumab + ipilimumab (n=300)	PDC (n=284)
	Grade 3-4	Grade 3-4
Total subjects with an event	159 (53.0)	121 (42.6)
≥ 1% of patients in any treatment group		
General disorders and administration site conditions	**29 (9.7)**	**30 (10.6)**
Fatigue	9 (3.0)	5 (1.8)
Pyrexia	4 (1.3)	2 (0.7)
Asthenia	4 (1.3)	12 (4.2)
Oedema peripheral	0	0
Non-cardiac chest pain	(1.7)	1 (0.4)
Chest pain	4 (1.3)	3 (1.1)
Pain	0	2 (0.7)
Malaise	2 (0.7)	0
Mucosal inflammation	0	2 (0.7)
Peripheral swelling	0	
General physical health deterioration	0	3 (1.1)
Gastrointestinal disorders	**28 (9.3)**	**21 (7.4)**
Diarrhoea	12 (4.0)	2 (0.7)
Nausea	2 (0.7)	7 (2.5)
Constipation	1 (0.3)	2 (0.7)
Vomiting	0	6 (2.1)
Abdominal pain	2 (0.7)	2 (0.7)

Event, n (%)	Nivolumab + ipilimumab (n=300) Grade 3-4	PDC (n=284) Grade 3-4
Colitis	7 (2.3)	1 (0.4)
Respiratory disorders	**27 (9.0)**	**17 (6.0)**
Dyspnoea	7 (2.3)	9 (3.2) 0
Cough	2 (0.7)	0
Pleural effusion	3 (1.0)	2 (0.7)
Pneumonitis	3 (1.0)	0
Hiccups	0	0
Pulmonary embolism	3 (1.0)	3 (1.1)
Skin and tissue disorders	**12 (4.0)**	**1 (0.4)**
Pruritus	3 (1.0)	0
Rash	3 (1.0)	0
Rash maculo-papular	2 (0.7)	0
Dry skin	0	0
Infections and infestations	**25 (8.3)**	**12 (4.2)**
Nasopharyngitis	1 (0.3)	0
Pneumonia	8 (2.7)	5 (1.8)
Lower respiratory tract infection	3 (1.0)	1 (0.4)
Metabolism and nutrition disorders	**22 (7.3)**	**21 (7.4)**
Decreased appetite	3 (1.0)	4 (1.4)
Hypoalbuminaemia	1 (0.3)	2 (0.7)
Hyponatraemia	5 (1.7)	4 (1.4)
Dehydration	3 (1.0)	2 (0.7)
Hypokalaemia	0	3 (1.1)
Musculoskeletal and connective tissue disorders	**13 (4.3)**	**2 (0.7)**
Arthralgia	3 (1.0)	0
Myalgia	0	0
Back pain	2 (0.7)	1 (0.4)
Pain in extremity	0	0
Musculoskeletal pain	2 (0.7)	0
Investigations	**32 (10.7)**	**9 (3.2)**
Blood creatinine increased	1 (0.3)	0

Event, n (%)	Nivolumab + ipilimumab (n=300) Grade 3-4	PDC (n=284) Grade 3-4
Lipase increased	16 (5.3)	1 (0.4)
Amylase increased	9 (3.0)	1 (0.4)
Alanine aminotransferase increased	6 (2.0)	0
Blood alkaline phosphatase increased	2 (0.7)	0
Weight decreased	0	1 (0.4)
Aspartate aminotransferase increased	5 (1.7)	0
Nervous system disorders	**15 (5.0)**	**2 (0.7)**
Headache	0	0
Dizziness	0	0
Dysgeusia	0	0
Syncope	4 (1.3)	1 (0.4)
Blood and lymphatic system disorders	**18 (6.0)**	**84 (29.6)**
Anaemia	8 (2.7)	39 (13.7)
Neutropenia	3 (1.0)	45 (15.8)
Thrombocytopenia	2 (0.7)	11 (3.9)
Leukopenia	0	8 (2.8)
Pancytopenia	0	5 (1.8)
Febrile neutropenia	0	3 (1.1)
Endocrine disorders	5 (1.7)	0
Hypothyroidism	0	0
Hypopituitarism	3 (1.0)	0
Psychiatric disorders	**2 (0.7)**	**2 (0.7)**
Insomnia	0	0
Anxiety	0	0
Injury, poisoning and procedural complications	**7 (2.3)**	**2 (0.7)**
Infusion related reaction	4 (1.3)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**12 (4.0)**	**5 (1.8)**
Malignant neoplasm progression	9 (3.0)	5 (1.8)
Cardiac disorders	**10 (3.3)**	**5 (1.8)**
Atrial fibrillation	2 (0.7)	3 (1.1)

Event, n (%)	Nivolumab + ipilimumab (n=300) Grade 3-4	PDC (n=284) Grade 3-4
Vascular disorders	12 (4.0)	1 (0.4)
Hypertension	6 (2.0)	1 (0.4)
Hepatobiliary disorders	**17 (5.7)**	**0**
Hepatic function abnormal	5 (1.7)	0
Immune-mediated hepatitis	3 (1.0)	0
Renal and urinary disorders	**9 (3.0)**	**2 (0.7)**
Acute kidney injury	5 (1.7)	0

Included events reported between the first dose of study drug and 30 days after the last dose of study drug.
Source: Table 11 from the response to clarification [4]

At the time of the database lock, 198 (66%) patients who were treated with nivolumab + ipilimumab had died, while 212 (75%) patients who received PDC had died.[2] In both treatment arms, disease progression was the most common cause of death.[2]

Table 3.12 shows the main causes of death.

Table 3.12: CheckMate-743: summary of deaths – all treated patients

Safety parameters, n (%)	Nivolumab + ipilimumab[a] (n=300)	Chemotherapy[b] (n=284)
Number of patients who died	198 (66.0)	212 (74.6)
Within 30 days of last dose	28 (9.3)	14 (4.9)
Within 100 days of last dose	55 (18.3)	50 (17.6)
Primary reason for death		
Disease	183 (61.0)	199 (70.1)
Study drug toxicity	3 (1.0)[c]	1 (0.4)[d]
Unknown	3 (1.0)	2 (0.7)
Other	9 (3.0)	10 (3.5)

Note: Person-years of exposure: nivolumab + ipilimumab, 220.3; chemotherapy, 94.5. Nivolumab + ipilimumab dosages were nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks.
[a] Median (interquartile range) doses for treated patients: nivolumab, 12.0 (5.0-23.5); ipilimumab, 4.0 (2.0-7.0).
[b] Median (interquartile range) doses for treated patients: pemetrexed, 6.0 (4.0-6.0); cisplatin 5.0 (3.0-6.0); carboplatin 6.0 (4.0-6.0).
[c] 3 deaths due to nivolumab + ipilimumab: pneumonitis, encephalitis, and acute heart failure.
[d] 1 death due to chemotherapy: myelosuppression.
Source: Table 20 of the CS.[2]

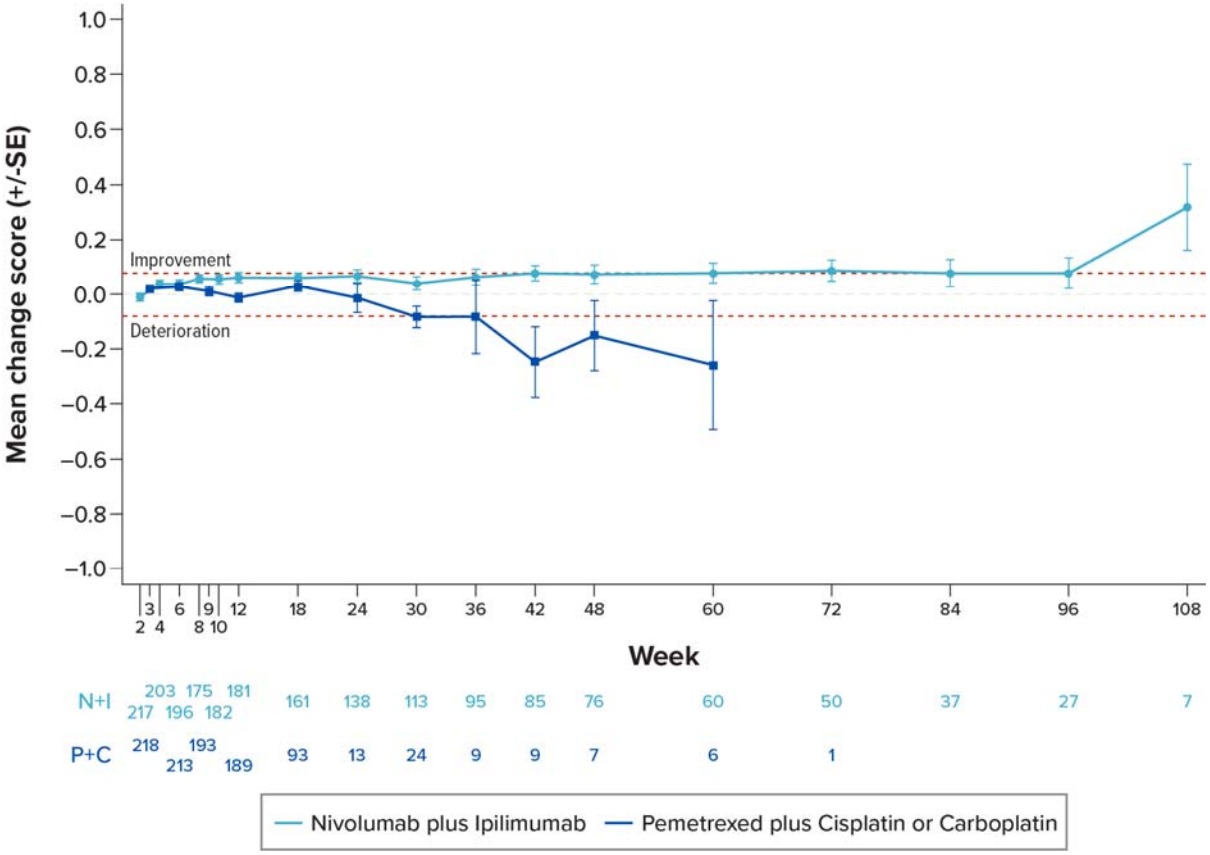
ERG comment: The rate of SAEs, treatment-related SAEs and AEs leading to discontinuation was considerably higher in patients treated with nivolumab + ipilimumab than for those in the PDC group. Although the rate of death was higher in the PDC group, three patients were reported to have died due to study drug toxicity in the nivolumab + ipilimumab arm: one of these died because of pneumonitis, for which there were also three Grade 3-4 events, respiratory tract infections also being more common

in the nivolumab + ipilimumab group than in the PDC group (See Table 3.12). A further patient in the nivolumab + ipilimumab group died of acute heart failure; there were also more Grade 3-4 cardiovascular events in the nivolumab + ipilimumab group than in the PDC group.

3.2.4.5 Health-related quality of life

The CS noted that patients who received first-line nivolumab + ipilimumab identified their HRQoL during the treatment period as stable or improved when compared to patients who received PDC and experienced deterioration in HRQoL during the treatment and follow-up periods.[2] In the current submission, HRQoL was measured using European Quality of Life-5 Dimensions 3 levels (EQ-5D-3L) Utility Index, EQ-5D-3L visual analogue scale (VAS), and Lung Cancer Symptom Scale–Mesothelioma (LCSS-Meso) scales.[2] According to the EQ-5D-3L Utility Index, patients treated with nivolumab + ipilimumab showed improved EQ-5D scores from 0.6959 at baseline to a peak score of 0.8529 at week 84.[2] Patients treated with PDC were observed to remain stable until week 30, after which EQ-5D scores indicated a deterioration from baseline, as depicted in Figure 3.3.[2] These changes were reported to have been clinically meaningful, having exceed the MID, defined as the smallest change considered to be clinically meaningful, has been estimated to be a change from baseline of 0.08 for the EQ-5D-3L Utility Index score.[2]

Figure 3.3: EQ-5D-3L Utility Index: mean change from baseline scores by treatment group (patient-reported outcome analysis population)



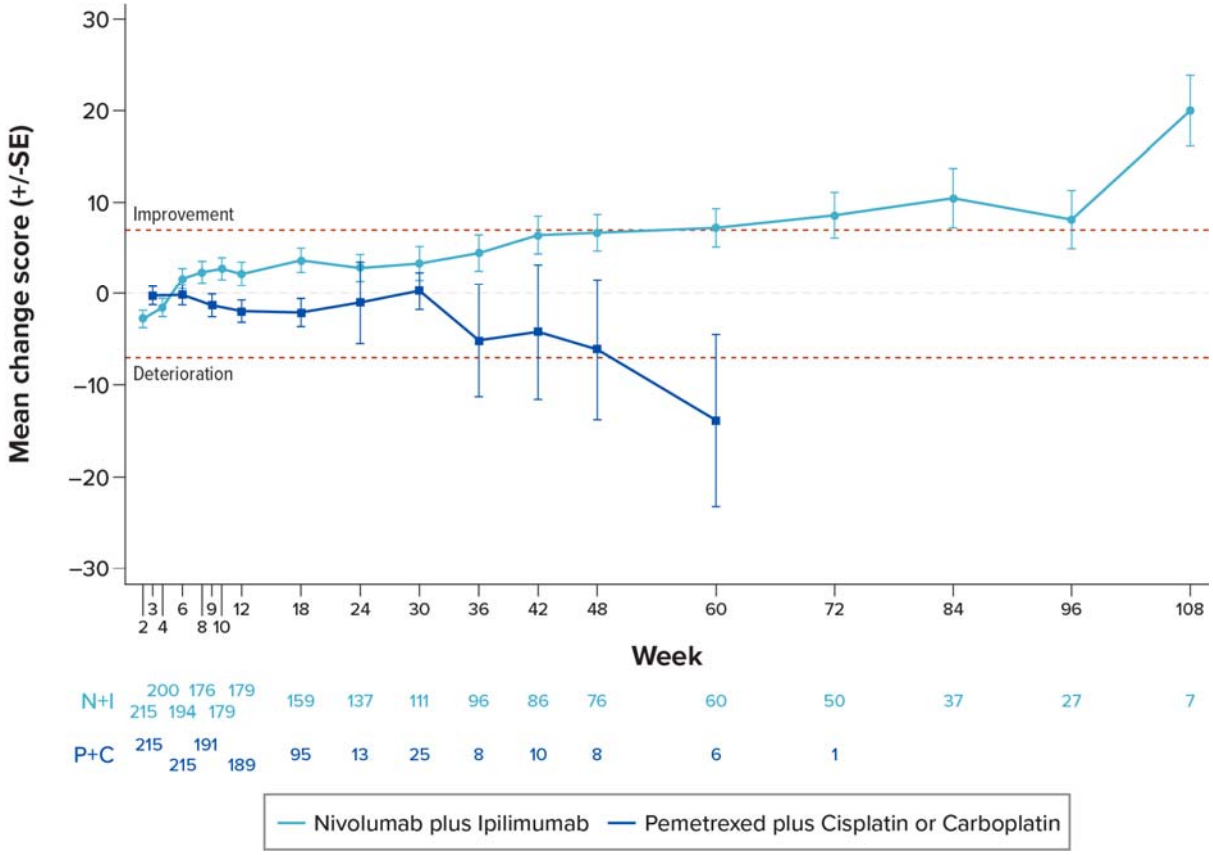
N+I = nivolumab + ipilimumab; P+C = pemetrexed + cisplatin or carboplatin; PRO = patient-reported outcome; SE = standard error.

Note: PRO analysis population includes all patients with EQ-5D baseline data and data at 1 or more postbaseline visits. The EQ-5D Utility Index score ranges from −0.594 to 1, with higher scores indicating better health state. Only time points with > 5 patients are shown.

Source: Figure 19 of the CS.[2]

The overall health of the patients was assessed using the EQ-5D VAS (see Figure 3.4).[2] There was an observed trend for improvement in the nivolumab + ipilimumab arm, which was identified as being clinically meaningful (greater than seven-point difference) from week 60.[2] Patients in the nivolumab + ipilimumab arm showed a clinically meaningful improvement in mean EQ-5D VAS scores from baseline, 69.9, to 82.7 at week 72.[2] A trend toward scores indicating deterioration was observed in the PDC arm from week 3 to week 24 and again from week 36 to week 60.[2] However, this trend was not determined to be clinically meaningful.

Figure 3.4: EQ-5D VAS: mean change from baseline scores by treatment group (patient-reported outcome analysis population)



N+I = nivolumab + ipilimumab; P+C = pemetrexed + cisplatin or carboplatin; PRO = patient-reported outcome; SE = standard error; VAS = visual analogue score.
Note: PRO analysis population includes all patients with EQ-5D baseline data and data at 1 or more postbaseline visits. The EQ-5D VAS score ranges from 0-100, with higher scores indicating better health state. Only time points with > 5 patients are shown.
Source: Figure 20 from the CS.[2]

According to the LCSS-Meso Average Symptom Burden Index (ASBI), patients treated with nivolumab + ipilimumab experienced a clinically meaningful improvement in mean score change from baseline to week 72.[2] During this time, patients in the PDC arm remained stable.[2] A similar pattern was observed for the LCSS-Meso 3IGI.[2]

ERG comment: The company described the change in EQ-5D (both 3L and VAS) as 'clinically meaningful'. It is not clear to the ERG why the decrease in EQ-5D VAS was not regarded as clinically meaningful given that it seemed to cross the seven-point threshold. Nevertheless, it does seem to be the case that the trend for nivolumab + ipilimumab indicated probable stability or improvement whereas that for PDC indicated probable deterioration.

3.2.4.6 Subsequent therapy

Subsequent systemic therapy was received by 44% and 41%; subsequent immunotherapy by 3% and 20%, and subsequent chemotherapy by 43% and 32% patients in the nivolumab + ipilimumab arm and in the PDC arm respectively, as reported in Table 6.5.3-1 in the CSR.[7]

ERG comment: The ERG asked the company to explain the differences between the two arms, with respect to the choice of subsequent therapy, and to discuss the likely implications of these differences for the relative effectiveness of nivolumab + ipilimumab vs. PDC. The ERG also requested evidence that the types of subsequent therapy in the trial are those that would also be used in England NHS practice or, if this is not the case, for the company to discuss the likely implications of any discrepancy. In response to clarification the company stated that the effect of any difference would probably be minimal given that survival on subsequent therapy is so short; they cited real-world data from the CAS registry of patients with unresectable MPM in England from January 2013-December 2017, which showed that median OS was 8.5 months from start of second-line therapy and median treatment duration of second-line therapy was 1.6 months.[4] However, the source provided and cited by the company did not report those numbers.[1] With the FAC, the company have subsequently provided the poster for that reference, which does report those figures. The company also argued that the type of subsequent therapy employed in the trial was likely to be representative of English NHS practice, again citing the same source as showing that of those who received a second-line therapy, 43.6% received second-line PDC (platinum + pemetrexed), 18.6% received second-line treatment in a clinical trial, and 24.1% received second-line vinorelbine. However, these figures could not be located by the ERG in that source.[1] Again, the poster provided with the FAC does report those figures. Nevertheless, they do appear to be quite different to those in the PDC arm of the CheckMate-743 trial of: pemetrexed (15.9%), vinorelbine (8.3%).[7] Therefore, there remains an issue as to both the effect of variation between arms and between the CheckMate-743 trial and English NHS practice.

3.2.5 Subgroup analyses

Subgroup analyses were conducted as specified in the NICE scope, i.e. according to PD-L1 status and histological subtype.

3.2.5.1 PD-L1 status

Table 3.13 shows the results of subgroup analyses by PD-L1 status. The nivolumab + ipilimumab arm among PD-L1 ≥ 1% produced a greater OS benefit than those with PD-L1 <1%.[2] The median OS among those treated with nivolumab +ipilimumab with PD-L1 <1% was 17.3 months (95% CI, 10.1to 24.3 months), whereas those treated with nivolumab + ipilimumab with PD-L1≥ 1% observed a median OS of 18.0 months (95% CI, 16.8 to 21.5 months).[2] Patients treated with PDC with PD-L1 <1% had a median OS of 16.5 months (95% CI, 13.4 to 20.5 months), whereas patients treated with PDC with PD-L1 ≥ 1% had a median OS of 13.3 months (95% CI, 11.6 to 15.4 months).[2]

When considering patients with PD-L1-positive tumours, nivolumab + ipilimumab appeared to have a beneficial effect on PFS (HR, 0.81; 95% CI, 0.64 to 1.01) when compared to patients treated with PDC. However, when considering patients with PD-L1 negative tumours, PFS favoured PDC (HR, 1.79 (95% CI, 1.21 to 2.64).[2] The company noted that the sizes of these groups were not balanced as 135 patients were included in the PD-L1 <1% group and 451 patients were in the PD-L1≥ 1% group.[2]

The ERG requested further information regarding the results of any formal statistical analyses for the comparison of all PD-L1 expression-related outcomes. However, the company reiterated all available results related to the PD-L1 subgroup had been presented.[4] The company also noted that PD-L1 was

not a stratification factor of the CheckMate-743 trial and was limited by potential imbalances in known or unknown prognostic factors.[4] Due to the small sample size and event counts in the PD-L1 negative subgroup, statistical analyses should be interpreted with caution.[4]

Table 3.13: Subgroup analyses by PD-L1 status

Outcome	PD-L1 < 1% (n=135)		PD-L1 ≥ 1% (n=451)	
	Nivolumab + ipilimumab (n=57)	PDC (n=78)	Nivolumab + ipilimumab (n=232)	PDC (n=219)
OS				
Median OS (95% CI), months[a]	17.3 (10.1-24.3)	16.5 (13.4-20.5)	18.0 (16.8-21.5)	13.3 (11.6-15.4)
HR[b] (95% CI) vs. PDC	0.94 (0.62-1.40)		0.69 (0.55-0.87)	
No. of events	40	58	150	157
PFS by BICR				
Median PFS[a] (95% CI), months	4.1 (2.7-5.6)	8.3 (7.0-11.1)	7.0 (5.8-8.5)	7.1 (6.2-7.6)
HR[b] (95% CI) vs. PDC	1.79 (1.21-2.64)		0.81 (0.64-1.01)	
No. of events	50	53	156	152
ORR per BICR				
ORR,[c] % (95% CI)	21.1 (11.4-33.9)	38.5 (27.7-50.2)	43.5 (37.1-50.2)	44.3 (37.6-51.1)
Best overall response, n (%)				
CR	0	0	3 (1.3)	0
PR	12 (21.1)	30 (38.5)	98 (42.2)	97 (44.3)
Stable disease	28 (49.1)	38 (48.7)	79 (34.1)	84 (38.4)
Progressive disease	16 (28.1)	6 (7.7)	37 (15.9)	8 (3.7)

Source: Table 15, CS.[2]
BICR = blinded independent central review; CI = confidence interval; CR = complete response; HR = hazard ratio; ORR = objective response rate; OS = overall survival; PDC = platinum-based doublet chemotherapy; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response.
[a] Kaplan-Meier estimates.
[b] Unstratified Cox proportional hazard model.
[c] Number of (CR+PR) ÷ number of patients. CI based on the Clopper and Pearson method.

3.2.5.2 Histological subtype

Table 3.14 shows the results of analyses by histological subtype; this table was populated from Appendix F.[6]

The company noted that patients treated with nivolumab + ipilimumab demonstrated an improved OS when compared to patients treated with PDC.[2] Patients treated with nivolumab + ipilimumab were noted to have a similar median OS across histologies.[2] Those with epithelioid MPM had a median OS of 18.7 months, whereas those with non-epithelioid MPM had a median OS of 18.1 months.[2] For patients treated with PDC, the median OS was observed to be lower in the non-epithelioid subgroup when compared to the epithelioid subgroup, 8.8 and 16.5 months, respectively.[2]

In patients treated with nivolumab + ipilimumab, who had non-epithelioid MPM, an improved PFS was identified when compared with treatment with PDC (HR, 0.58; 95% CI, 0.38-0.90).[2] In patients treated

with PDC, with epithelioid MPM, PFS improved over nivolumab + ipilimumab (HR, 1.14; 95% CI, 0.92 to 1.41). However, when considering patients treated with nivolumab + ipilimumab, the median PFS was noted to be of a longer duration, 8.31 months, in the non-epithelioid subgroup when compared to the epithelioid subgroup, 6.18 months.[2] In patients treated with PDC, the median PFS was shorter in the non-epithelioid subgroup, 5.59 months, when compared to the epithelioid subgroup, 7.66 months.[2]

The ERG requested further clarification regarding the results of subgroup analyses by histological subtype for response outcomes. In the response to clarification, the company stated that the assessment of outcomes by more specific non-epithelioid subgroups was limited due to the small number of patients in each non-epithelioid subtype.[4] The company also noted that formal statistical analyses were not done.[4] The company stated in their response to clarification that in real-life clinical practice in the UK, a high proportion of patients with MPM have unknown or not otherwise specified histology.[4] However, the company emphasised that the treatment effect of nivolumab + ipilimumab versus PDC was consistent across the histological subtypes.[4]

Table 3.14: Subgroup analyses by histological subtype

	Non-epithelioid (n=149)		Epithelioid (n=456)	
Outcome	**Nivolumab + ipilimumab (n=74)**	**PDC (n=75)**	**Nivolumab + ipilimumab (n=229)**	**PDC (n=227)**
OS				
Median OS (95% CI), months[a]	18.07 (12.16-22.77)	8.80 (7.43-10.15)	18.73 (16.92-21.98)	16.49 (14.88-20.47)
HR[b] (95% CI) vs. PDC	0.46 (0.31-0.68)		0.86 (0.69-1.08)	
No. of events	50	63	150	156
PFS by BICR				
Median PFS[a] (95% CI), months	8.31 (4.11-10.25)	5.45 (5.09-6.80)	5.98 (5.39-6.97)	7.75 (7.16-8.34)
HR[b] (95% CI) vs. PDC	0.56 (0.37-0.85)		1.16 (0.93-1.45)	
No. of events	51	54	167	155
ORR per BICR				
ORR,[c] % (95% CI)			38.4 (32.1-45.1)	47.6 (40.9-54.3)

Sources: Figures 4 and 5, Table 13, Appendix F.[6].
BICR = blinded independent central review; CI = confidence interval; CR = complete response; HR = hazard ratio; ORR = objective response rate; OS = overall survival; PDC = platinum-based doublet chemotherapy; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response.
[a] Kaplan-Meier estimates.
[b] Unstratified Cox proportional hazard model.
[c] Number of (CR+PR) ÷ number of patients. CI based on the Clopper and Pearson method.

ERG comment: In terms of OS, nivolumab + ipilimumab appears to be clearly more effective than PDC in patients with MPM with PD-L1 ≥ 1% and in patients with MPM with non-epithelioid histology. Although not so clear and with a reduced difference, nivolumab + ipilimumab also appears to be more effective than PDC, for epithelioid histology. There appears to be little difference between treatments for PD-L1 < 1%.

In terms of PFS, nivolumab + ipilimumab appears to be clearly more effective than PDC for MPM with non-epithelioid histology. Although not so clear and with a reduced difference, nivolumab + ipilimumab also appears to be more effective than PDC for MPM with PD-L1 ≥ 1%. Nivolumab + ipilimumab appears to be clearly less effective than PDC for MPM with PD-L1 < 1%. Although not so clear and with a reduced difference, nivolumab + ipilimumab also appears to be less effective than PDC for MPM with epithelioid histology.

There remains a question about the potential interaction effects of these two clinically relevant subgroups; no data are available for subgroup combinations, e.g. PD-L1<1% and epithelioid histology. This factor, in combination with data immaturity, means that there remains uncertainty as to the relative effectiveness of the intervention in clinically relevant subgroups.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Because only one RCT was included, no indirect comparisons were performed.[2]

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Because only one RCT was included, no indirect comparisons were performed.[2]

3.5 Additional work on clinical effectiveness undertaken by the ERG

None.

3.6 Conclusions of the clinical effectiveness section

The CS included a systematic review, which appears to have been largely well conducted.[2] This probably included more studies than are required if one considers that the most appropriate evidence is the CheckMate-743 trial, given that this can be assumed to be the only trial that compares the intervention to PDC and assuming that PDC is the only relevant comparator. The CheckMate-743 trial is an RCT that compares nivolumab + ipilimumab with PDC in MPM, the population specified in the scope, the primary outcome being OS, but also reporting all other outcomes listed in the scope including ORR, PFS, HRQoL and AEs. The population in CheckMate-743 was narrower than that of the scope, including only patients with ECOG PS 0-1, but the company confirmed that this was the population that they wanted to be considered in this appraisal. The quality of the RCT was diminished by the lack of blinding: other than that, it could be regarded as of high quality. As discussed in Section 2.2, there is also a discrepancy between the dosing of nivolumab in the trial, which was weight-based, and that of the proposed marketing authorisation, which will be fixed. The ERG did request evidence that this difference in dosing will have no effect on effectiveness, quality of life or safety.[3] However, although the company's response does provide some reassurance regarding safety, a judgment of safety/tolerance is not a substitute for actual AE rates at the given fixed dose.[4] The presentation also provided by the company stated that: *"…efficacy and safety were evaluated by characterizing the relationships between simulations of NIVO exposure and OS or grade ≥ 2 immune-mediated adverse events (grade 2+ IMAEs), respectively, using the multivariate Cox proportional-hazard model*".[5] However, it is not clear to the ERG precisely how outcomes could be estimated for a fixed dose without evidence from patients who received that dosing regimen. Subgroup analyses by weight were also provided, but again these do not show the effect of patients receiving a lower or higher dose, as would have been the case if dosing had been weight-based.[5] Therefore, an issue remains regarding the effectiveness and safety of the expected licensed dose of nivolumab.

The ability to inform a comparison with any specific form of PDC was also affected by there being IC of either carboplatin or cisplatin. Whilst such a choice is consistent with clinical practice, because only 38 patients were from the UK and the extent to which the choice of cisplatin and carboplatin would be in accordance with English NHS practice is uncertain and there remains a question both of the applicability of the comparator, as discussed in Section 2.3, and the trial generally to English NHS practice.

At the time of the interim analysis with a database lock of 3 April 2020, a statistically significant OS benefit was observed for patients who were treated with nivolumab + ipilimumab when compared to patients treated with PDC.[2] However, there was no statistically significant difference in PFS and results for ORR were similar.[2] The ERG did request results from a more recent data cut, but the company replied: "*As CheckMate-743 met its primary endpoint at the 3 April 2020 database lock, this analysis was considered the final analysis. However, follow up of CM-743 is ongoing and additional data cuts are expected, likely in Q2/Q3 2021 (TBC). As the timing of the analysis is event driven, there is uncertainty on the exact timing of future database locks*."[4] Although it is unlikely that the results will change the interpretation that nivolumab + ipilimumab is more effective in terms of OS, the precise size of the difference might be important particularly in determining whether nivolumab + ipilimumab is cost effective. The interpretation of PFS results may change, given that progression data are incomplete. This data immaturity therefore remains an issue.

The ERG asked the company to explain the differences between the two arms of the CheckMate-743 trial, in the choice of subsequent therapy, and to discuss the likely implications of these differences for the relative effectiveness of nivolumab + ipilimumab vs. PDC. The ERG also requested evidence that the types of subsequent therapy used in the trial are those that would also be used in English NHS practice or, if this is not the case, to discuss the likely implications of any discrepancy. In response to clarification the company stated that the effect of any difference would probably be minimal given that survival is so short on subsequent therapy.[4] However, the source provided by the company in response to clarification does not seem to provide those data to support this statement.[1] The company also argued that the type of subsequent therapy employed in the trial was likely to be representative of English NHS practice.[4] However, again the figures mentioned by the company could not be located by the ERG in that same source and they do appear to be quite different to those in the PDC arm of the CheckMate-743 trial in terms of pemetrexed and vinorelbine use.[7] Therefore, there remains an issue as to the effect of variation in subsequent therapy, both between arms and between the CheckMate-743 trial and English NHS practice.

The subgroup analyses specified in the scope, according to PD-L1 status and histology, were performed and did indicate some important variation in the effectiveness of nivolumab + ipilimumab versus PDC. [redacted] There remains a question about the potential interaction effects of these two

clinically relevant subgroups; no data are available for subgroup combinations, e.g. PD-L1<1% and epithelioid histology. This factor, in combination with data immaturity, means that there remains uncertainty as to the relative effectiveness of the intervention in clinically relevant subgroups.

4. COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the CS. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness section

Appendix H and I of Document C report details of an updated SLR to identify evidence about cost effectiveness, HRQoL and healthcare resource use for patients with MPM. All databases were searched from inception to 5 October 2020. Searches of NHS EED and DARE were originally undertaken in March 2018. These searches were not updated as these databases are no longer being added to. Appendix H reported searches undertaken for economic evaluations for MPM while Appendix I reported searches for HRQoL and utilities for MPM. No language limits were reported in the search strategies. A cost filter, however, was applied to 2018 searches of NHS EED which may have compromised the retrievability of potentially relevant studies. A summary of sources searched is provided in Table 4.1.

Table 4.1: Data sources for the cost effectiveness systematic review

	Resource	Host/source	Date ranges	Dates searched
Electronic databases	Embase	Embase.com	From inception	5.10.20
	MEDLINE	Embase.com		5.10.20
	NHS Economic Evaluations Database (NHS EED)	Wiley		9.5.18
	Database of Abstracts of Reviews of Effects (DARE)	Wiley		9.5.18
	MEDLINE In-Process and Ahead of print	PubMed		5.10.20
	EconLit	AEAweb.org		5.10.20
	International HTA Database			5.10.20
Conference proceedings	ASCO	https://meetinglibrary.asco.org/results/(Keywords:"Mesothelioma");page=0	2018-2020	October 2020
	ESMO	https://www.sciencedirect.com/search?qs=mesothelioma&pub=Annals%20of%20Oncology&cid=321639&years=2020&lastSelectedFacet=years	2018-2020	
	AACR	https://www.aacr.org/professionals/meetings/previous-aacr-meetings/previous-aacr-meetings-2018/	2018	

		https://www.aacr.org/professionals/meetings/previous-aacr-meetings/previous-aacr-meetings-2019/	2019	
		https://www.aacr.org/meeting/aacr-annual-meeting-2020/abstracts/ https://cancerres.aacrjournals.org/content/80/16_Supplement	2020	
	ISPOR	https://www.ispor.org/heor-resources/presentations-database/search	2018-2020	
	WCLC	https://wclc2018.iaslc.org/wp-content/uploads/2018/09/WCLC2018-Abstract-Book_vF-LR-REV-SEPT-25-2018.pdf	2018	
		https://wclc2019.iaslc.org/wp-content/uploads/2019/08/WCLC2019-Abstract-Book_web-friendly.pdf	2019	
	ELCC	https://www.jto.org/issue/S1556-0864(18)X0004-5	2018	
		https://www.sciencedirect.com/journal/annals-of-oncology/vol/30/suppl/S2?page=3#article-201	2019	
	IMIG	Not searched		

Additional resources
National Institute for Health and Care Excellence (NICE)
Scottish Medicines Consortium (SMC)
Institute for Quality and Efficiency in Health Care (IQWiG)
Autorité de Santé (HAS)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Pharmaceutical Benefits Advisory Committee (PBAC)
Food and Drug Administration (FDA)
European Medicines Agency (EMA)
Gesellschaft der Epidemiologischen Krebsregister in Deutschland (GEKID)
Belgian Cancer Registry
Dutch Cancer Registry
Italian Association of Cancer Registries (ITACAN)
Red Española de Registros de Cáncer (REDECAN)
Nordic Cancer Registry (NORDCAN)
Surveillance, Epidemiology, and End Results Program (SEER)
National Lung Cancer Audit annual report

ERG comment

- The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were searched, including additional grey literature resources. Reference checking was also undertaken.
- Searches overall were well-conducted and were transparent and reproducible.
- No date limits were unnecessarily applied. There was an English language restriction, but this was not applied at the searching stage.
- Cochrane Library searches conducted in March 2018 of NHS EED and DARE applied a cost filter (Appendix H). NHS EED is a database of cost evaluations and applying an additional filter will have affected the retrievability of possibly relevant records and is not recommended.[14] In response to clarification, the company confirmed that one search strategy had been used to search Cochrane Library databases and that filters had been applied to "maximise sensitivity and precision" as CENTRAL also includes cost publications. However, the ERG is concerned that the unnecessary application of a filter to a pre-filtered resource such as NHS EED compromised the sensitivity of finding potentially relevant cost studies and that this resource should have been searched separately without the application of a filter.

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies, HRQoL studies and costs and resource use studies were not clearly presented in the CS, but are included in the flow charts of the three reviews in Figures 6-8 in Appendix H.[6]

ERG comment: The ERG was unsure whether the applied eligibility criteria were suitable to fulfil the company's objective to identify cost effectiveness studies in this disease area as explanations for some exclusion criteria were lacking, namely for: "Line of treatment unclear", "No SGA disease" and "No SGA LOT". The company provided justification and explanation in response to clarification question B1 and the ERG was satisfied that it was unlikely that any studies were missed.[4]

4.1.3 Conclusions of the cost effectiveness review

A total of 23 economic evaluation studies were identified, including nine with cost effectiveness analyses, which are presented in Table 24 of the CS; one more study was added in Table 21 in Appendix H. These 10 studies were summarised in Appendix H. None of these 10 economic evaluations considered nivolumab + ipilimumab for the treatment of MPM. There are only few published economic evaluations of treatments for MPM. The company also stated that *"the majority of published analyses have considered the combination treatment of pemetrexed plus cisplatin. Past analyses have been limited in scope, both in terms of time horizon and the inclusion of all relevant comparators. There is no apparent established modelling methodology at this stage, with previous analyses having adopted various approaches (from simple trial-based analyses which do not distinguish between progression-free and progressed disease, to partitioned survival modelling and Markov modelling). Preference-based quality of life data to provide utility values for cost-effectiveness analyses is a crucial data gap."*[2]

ERG comment: Eligibility criteria were suitable for the SLR performed. The CS provides an acceptable overview of the included cost effectiveness, HRQoL and resource use and costs studies.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.2: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	In line with reference case
Perspective on costs	NHS and PSS	In line with reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	In line with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	In line with reference case
Synthesis of evidence on health effects	Based on systematic review	In line with reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	In line with reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	In line with reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	In line with reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	In line with reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	In line with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	In line with reference case

EQ-5D = Euroqol-5D; NHS = National Health Service; PSS = personal and social services; QALY = quality-adjusted life year; UK = United Kingdom

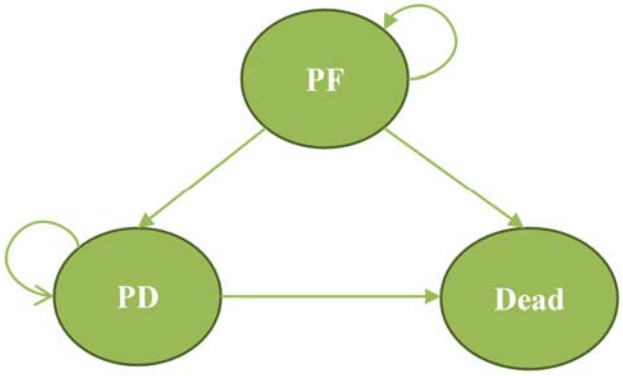
4.2.2 Model structure

The analysis was based on a three-health state partitioned survival model, using a cycle time of one week to accommodate the administration cycles for therapies considered in the model. The model was developed in Microsoft Excel and programmed using standard Excel functions, where possible.

The states in the model are progression free (PF), progressed disease (PD), and dead (Figure 4.1). The three health states represent the primary stages of disease in MPM: PF with first-line treatment, the occurrence of disease progression, and death. These health states correspond to the primary and secondary endpoints of the CheckMate-743 trial. This model structure is consistent with the approaches adopted in previous published economic evaluations within MPM and previous NICE technology appraisals of oncology products.

Patients enter the model in the PF health state. At the end of each cycle, the proportion of patients in PF, PD, and dead is calculated from parametric survival curves for PFS and OS estimated from the CheckMate-743 trial. Specifically, the number of patients occupying each state in the model is derived directly from the cumulative survival probabilities of PFS and OS (area under the curve approach), with the proportion of patients in the PD health state being calculated as the difference between OS and PFS (see CS Figure 25).[2]

Figure 4.1: Model structure



Source: Based on CS Figure 24[2]

ERG comment: The main concern of the ERG relates to the use of a partitioned survival model given the issues highlighted in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19.[15]

In clarification question B4 the company was asked to justify the use of a partitioned survival model given the issues highlighted in NICE DSU TSD 19 and to use state transition modelling to assist in verifying the plausibility of the partitioned survival model extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11).[15] This company justified the use of the partitioned survival model based on European advisory board for the economic modelling, indicating that most advisors agreed with a partitioned survival model being used. Moreover, the company responded that it is unlikely that using a state transition model would have a large impact on outcomes as 1) post-progression treatments are administered for a short duration in this indication and 2) state transition models, in general, per se do not necessarily result in different results compared to partitioned survival models. The company did not however provide supporting evidence that the difference in this specific case would be minimal, it is unclear to the ERG why the duration of post-progression treatments is mentioned as an argument by the company. Hence the impact of the limitations related to the partitioned survival model (highlighted in NICE DSU TSD 19), such as the extrapolations of PFS and OS while assuming structural independence between these endpoints, is unclear. This is particularly relevant given the large proportion of (PF)LY that is accumulated beyond the observed data (see Section 5.1).

4.2.3 Population

The economic evaluation considers nivolumab + ipilimumab in the first-line treatment of adults with untreated unresectable MPM. The company stated that this was consistent with the study population of CheckMate-743, the decision problem and the anticipated licensed indication. No subgroup analyses were presented.

ERG comment: The main concerns of the ERG relate to: a) the population being narrower than the scope; and b) no subgroups being presented despite being listed in the scope.

a) The population in CheckMate-743 was narrower than that of the scope, limiting eligible patients to those with an ECOG status 0-1. The company clarified that no formal restriction with respect to ECOG status is made, as for many patients the ECOG status is unrecorded (see Section 2.1 of this report).
b) The company did not present subgroup cost effectiveness analyses despite relevant subgroups being listed in the scope, such as histologic subtype (epithelioid, sarcomatoid, biphasic) and level of PD-L1 expression. In response to clarification question B3, the company explained that it did *"not consider economic modelling of nivolumab + ipilimumab by histological subtype or PD-L1 expression as appropriate, given the high clinical unmet need of all patients with unresectable MPM eligible for SACT and the OS benefit seen in all subgroups in CheckMate-743."*[4] The company also considered the clinical data that was presented in the CS for the histological and PD-L1 subgroups in CheckMate-743 as descriptive in nature and that it should be interpreted with caution. Section 3.2.5 provides further detail on this issue. The ERG concludes that cost effectiveness may vary by subgroup.

4.2.4 Interventions and comparators

The intervention considered in the CS was nivolumab + ipilimumab, administered at a flat nivolumab dosage of 360 mg every three weeks, aligning with the anticipated EMA licence. This differs from the nivolumab weight-based dosage of 3 mg/kg every two weeks used in CheckMate-743. Ipilimumab is administered every six weeks at 1 mg/kg, which is in line with CheckMate-743. The CS includes a two-year stopping rule for nivolumab + ipilimumab, which is also in line with CheckMate-743.

The comparator considered was pemetrexed (500 mg/m2 every three weeks for six treatment cycles) + cisplatin (75 mg/m2 every three weeks for four treatment cycles) or carboplatin (550 mg/m2 every three weeks for four treatment cycles). According to the CS, pemetrexed + cisplatin or carboplatin is considered the standard of care therapy in the UK and is consistent with the comparator arm of the CheckMate-743 clinical trial.

The NICE scope also listed BSC and raltitrexed + cisplatin (for people for whom treatment with pemetrexed is unsuitable) as comparators, but these were not included. The company justified the selection of the comparators considering that raltitrexed was not approved for use in the UK for the first-line treatment of MPM and was not used in the NHS according to UK registry data and expert opinion. BSC was not considered an appropriate comparator because nivolumab + ipilimumab relates to a particular group of fit patients for whom BSC would not be deemed acceptable or ethical unless specifically requested by the patient.

ERG comment: The main concerns of the ERG relate to: a) the omission of potentially relevant comparators listed in the NICE scope (BSC and raltitrexed + cisplatin); b) the dosage differs between

this submission and the evidence; c) the use of a two-year stopping rule; d) pemetrexed + cisplatin and pemetrexed + carboplatin could be considered separate comparators.

a) The omission of potentially relevant comparators listed in the NICE scope (BSC and raltitrexed + cisplatin). As detailed in Section 2.3 of this report, the exclusion of BSC and raltitrexed + cisplatin was justified by the company and the ERG agrees that this is acceptable.
b) The dosage differs between this submission (which is in line with the anticipated marketing authorisation) and the evidence from CheckMate-743. As detailed in Section 2.2 of this report, uncertainty remains regarding the effectiveness and safety of the expected licensed dose of nivolumab.
c) The use of a two-year stopping rule for nivolumab + ipilimumab in the CS was in line with the evidence from CheckMate-743. It should be noted that [redacted] as shown in Figure 10 in Appendix K of the CS, despite the stopping rule stipulated in the study protocol. The impact of this on cost effectiveness results (particularly on costs) would be likely small, but it could be an important issue should this occur for further patients or should the stopping rule not be adhered to in clinical practice. The ERG therefore considers it important to explore whether more patients continued nivolumab + ipilimumab beyond 24 months and how long they continued treatment in future analyses.

4.2.5 Perspective, time horizon and discounting

The analysis was performed from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is one week to accommodate the administration cycles of the included therapies, with a lifetime time horizon (20 years), and a half-cycle correction was applied.

ERG comment: In the CS, the company states a 20-year time horizon was used, and the model continues until patients reach the age of 88 years (less than 1% of patients are still alive). This was considered to represent a lifetime time horizon. The approach is in concordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main source of evidence on treatment effectiveness used for intervention and comparators is the April 2020 database lock of CheckMate-743 (minimum follow-up for all patients was 22.1 months; 23% and 15% of patients treated with nivolumab + ipilimumab and PDC, respectively were still alive at this point). To estimate PFS and OS over the 20-year time horizon, parametric survival curves were fitted to CheckMate-743 patient-level data and used to extrapolate survival beyond the study time horizon.

4.2.6.1 Fitting and selecting procedure of the parametric survival models

Seven parametric models were considered for the extrapolation of PFS and OS (exponential, Weibull, Gompertz, log normal, log-logistic, gamma, and generalised gamma). The process for fitting and selecting parametric survival models was based on methods guidance from the Decision Support Unit at NICE and illustrated in CS Figure 26. This process included:

1. Assessing the proportional hazards assumption by examining the scaled Schoenfeld residuals (and Grambsch and Therneau's correlation test), log-cumulative hazards, log-cumulative odds, and standardised normal curve plots. In case of (non-)proportional hazards parametric survival models were (in)dependently estimated for both treatments (i.e. nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin).

2. Assessing fit to the observed data by examining goodness-of-fit statistics (AIC/BIC). This includes using rules of thumb that indicate that models that have an AIC/BIC of <4/<2 higher than the lowest AIC/BIC are considered the best fitting models based on the Burnham and Anderson rule of thumb (AIC) and Raftery rule of thumb (BIC)[16, 17].
3. Assessing clinical plausibility and external validation of the extrapolated survival estimates by considering data from the systemic anticancer therapy (SACT) population with newly diagnosed MPM from the Cancer Analysis System (CAS)[1] and the MAPS trial investigating bevacizumab + pemetrexed + cisplatin compared with pemetrexed + cisplatin for the treatment of patients with newly diagnosed unresectable MPM [18]. Particularly, the survival function as well as the shape of the hazard function were considered. Additionally, UK clinical experts were consulted on the expected survival with current treatments. The clinical input received indicated that five-year survival would be expected at 5%, 7.5-year survival at 2%, and 10-year survival at 0-2%.

4.2.6.2 Overall survival

The fitting and selecting procedure for OS is described considering the above-mentioned three criteria (see also CS Table 32).

1. **Proportional hazards assumption.** Based on CS Figure 30, non-proportional hazards were assumed, and the parametric survival models were fitted separately for both nivolumab + ipilimumab and PDC.
2. **Fit to the observed data.** For nivolumab + ipilimumab based on statistical goodness-of-fit and the abovementioned rules of thumb, the parametric survival models with the *Weibull, gamma and Gompertz distributions* might be considered the best fitting models (i.e. difference in AIC/BIC of <4/<2 compared with the lowest AIC/BIC; the *generalised gamma distribution* as well when only considering the AIC), see CS Table 28. For PDC these were the parametric survival models with the *gamma and log-logistic distributions* (the *generalised gamma and Weibull distributions* as well when only considering the AIC), see CS Table 30.
3. **Clinical plausibility and external validation of the extrapolated survival.** It was considered that, for both treatments, the modelled **hazard function** of the selected distribution should have an initial increase in hazards followed by long-term decreasing hazards (based on CS Figure 28, derived from MAPS data; according to clarification response B6 smoothed hazard plots based on CheckMate-743 and SACT data provided similar shapes for the hazard function). This was only observed for the parametric survival models using the *log-logistic and log-normal distributions* and for PDC using the *generalised gamma distribution* as well (though the decline of the hazard over time was smaller than for the log-logistic and log-normal distributions).
   Parametric survival models with distributions with **predicted survival** for PDC slightly below the survival observed in MAPS are appropriate; predictions aligned with the MAPS data were considered neutral, and predictions above or significantly below survival in MAPS were considered inappropriate. For nivolumab + ipilimumab, predicted survival that is lower than that observed for PDC in MAPS was considered inappropriate. Based on this criterion, *the log-logistic and log-normal distributions* were appropriate for nivolumab + ipilimumab while these were *the exponential, log-logistic and generalised gamma distributions* for PDC.

Based on these findings, the company selected a piecewise approach combining Kaplan-Meier (KM) data (up to the 22 months break point) with independently estimated parametric survival models for extrapolation (i.e. assuming non-proportional hazards). The selected parametric survival models were based on the log-logistic and exponential distributions for nivolumab + ipilimumab and PDC

respectively. The 22 months break point was selected as it was the approximate minimum patient follow-up at the database lock of CheckMate-743, and most censoring in the OS data in both treatment arms occurred after this point (see CS Figure 12).

4.2.6.3 Progression-free survival

The fitting and selecting procedure for PFS is described considering the above-mentioned three criteria.

1. **Proportional hazards assumption.** Based on CS Figure 30, non-proportional hazards are assumed, and the parametric survival models are fitted separately for both nivolumab + ipilimumab and PDC.
2. **Fit to the observed data.** For nivolumab + ipilimumab based on statistical goodness-of-fit and the abovementioned rules of thumb, the parametric survival model with the *generalised gamma distribution* might be considered the best fitting models (i.e. difference in AIC/BIC of <4/<2 compared with the lowest AIC/BIC), see CS Table 33. For PDC this was the parametric survival model with the *log-logistic distribution*, see CS Table 35.
3. **Clinical plausibility and external validation of the extrapolated survival.** The validation of this criterion for PFS is not explicitly described in the CS. Notably, the company stated that for PFS the selection of the parametric survival models was primarily guided by statistical and visual fit to the CheckMate-743 data for both treatment arms. As it has been shown previously that PFS for immunotherapies does not follow the same pattern as for other oncology treatments, the MAPS data were not considered appropriate for validating PFS for nivolumab + ipilimumab.

Based on these findings, the company selected parametric survival models with the generalised gamma and log-logistic distributions for nivolumab + ipilimumab and PDC respectively. If PFS is greater than OS at any time, the PFS is assumed to be equivalent to OS to avoid inconsistencies between OS and PFS.

4.2.6.4 Potential waning of treatment effect

In the CS base-case no treatment waning was assumed, i.e. the PFS and OS were assumed to be different for nivolumab + ipilimumab and PDC for the whole duration of the time horizon.

ERG comment: The main concerns of the ERG relate to: a) the approach to estimate OS; b) plausibility of long-term extrapolation of PFS; c) assuming no treatment waning in the CS base-case.

a) The selection of a piecewise approach to estimate OS for both nivolumab + ipilimumab and PDC was clarified in response to clarification question B5. Here the company stated: "*The decision to utilise a piecewise model was primarily guided by the PDC arm. As presented in the CS, distributions with the best statistical and visual fit to the KM data for the PDC arm did not provide plausible long-term extrapolations. The chosen base-case distribution for PDC (exponential) provided the most plausible long-term extrapolation that was aligned with clinical expert input but had a relatively poor fit to the within-trial data (underestimating within-trial survival). Thus, to overcome this limitation for the within-trial period the piecewise approach was selected. The same issue of fit to the within-trial data was not seen to the same extent in the nivolumab + ipilimumab arm. However, for consistency the approach was applied to both arms in the model.*"[4] Although this clarifies the company's preference for the piecewise approach, using KM data up to 22 months to overcome poor fit to the observed data, the combination of the specific distributions (i.e. exponential and log-logistic) with the KM data is not clearly justified. These combinations might be evaluated differently than reported in CS

Table 32 for the different distributions (without using KM data up to 22 months). The ERG generally does not prefer using KM curves for economic models as it might overfit the trial data which seems suboptimal for decision-making in UK clinical practice. Moreover, NICE DSU TSD 21 on flexible methods for survival analysis highlights that the selected 22 months break point may be arbitrary and potentially importantly influence the results of an analysis. Finally, deviation from standard parametric survival models (opting for a piecewise approach) because of suboptimal fit to the observed data might not be warranted given the large majority of LY gains are accumulated beyond the observed data period (See Table 5.2)

In addition to the above, based on the company's response to clarification question B5c it became clear that the estimation and implementation of the piecewise models incorporated in the economic model deviate from common practice and the piecewise models described in NICE DSU TSD 21. The implemented piecewise models are using parametric survival models estimated from baseline (time = 0; using the full dataset) instead of being estimated specifically from the break point (of 22 months). This approach is flawed according to the ERG as these parametric survival models, estimated from baseline, are not intended to be used after the break point only as the proportion of patients surviving up to this break point (i.e. conditional survival) using these parametric survival models might differ from the conditional survival based on the KM curve.

Given the abovementioned limitations of the company's piecewise approach and the lack of justifications for the selecting the distributions for the piecewise approach, the ERG prefers to use a standard parametric approach to estimate OS in its base-case. Specifically, the log-logistic distribution for both treatment arms is considered a plausible alternative, as illustrated in CS Table 32 considering the goodness of fit (AIC and BIC), the appropriateness of the hazard function as well as survival extrapolations (i.e. aligned with the MAPS data). Moreover, the CS section "Heuristics for selection of survival extrapolation for OS based on external validation" describes identical hazard functions for both PDC and nivolumab + ipilimumab (i.e. the hazard function of the selected distribution should have an initial increase in hazards followed by long-term decreasing hazards) that is consistent with the log-logistic distribution. Therefore, the log-logistic distribution is used for both treatment arms in the ERG base-case.

b) Based on fit to the observed data, the company's selected approach to estimate PFS seems appropriate (using the generalised gamma distribution for nivolumab + ipilimumab and the log-logistic for PDC), these were also confirmed by clinical experts as described in response to clarification question B8. Moreover, the company provided justification for using different distributions for nivolumab + ipilimumab and PDC, highlighting the different mechanism of action that nivolumab + ipilimumab has compared to PDC. Notably, given the large majority of PFLY gains are accumulated beyond the observed data period (See Table 5.2), the plausibility of long-term extrapolation and PFS gains is arguably the most important criterion to consider. In response to clarification question B8, the company indicated that the estimated PFS for PDC was in line with MAPS trial data up to five years. The MAPS data were not considered appropriate for validating PFS for nivolumab + ipilimumab. Given the substantial uncertainty related to the plausibility of the extrapolated PFS, the ERG performed two scenario analyses to examine the impact of alternative assumptions, selected based on statistical goodness-of-fit, related to estimated PFS: 1) use log-logistic distributions for both treatment arms and 2) use generalised gamma distributions for both treatment arms.

c) In the CS base-case no treatment waning was assumed, i.e. the PFS and OS were assumed to be different for PDC and nivolumab + ipilimumab for the whole duration of the time horizon. The company justified this by stating *"there is long-term evidence of a robust and durable treatment effect lasting beyond discontinuation for immunotherapies"* (response to clarification

question B10)[4] and referring to a publication by Antonia et al.[19] considering four-year survival with nivolumab in patients with previously treated advanced non-small-cell lung cancer. Additionally, the company provided a scenario analysis where the treatment effect is assumed to start deteriorating at year five and then decrease linearly to no treatment effect at year 10. This scenario resulted in a substantial increase in the ICER which would most likely increase further when assuming no treatment effect at year five as for instance preferred by the committee in ID1585 considering nivolumab for treating squamous cell carcinoma of the head and neck; appraisal consultation document section 3.15[20]. Given that it is unclear whether assuming a continued treatment effect over the lifetime horizon of the model is plausible and the uncertainty related to the long-term extrapolations (only three patients were at risk at 36 months according to Table 13 in the clarification letter), treatment waning was assumed after five years in the ERG base-case. Although there is precedence to use the five-year treatment waning time point (as highlighted above), the ERG acknowledges that the selected time point is arbitrary.

4.2.7 Adverse events

The only source of evidence on treatment adverse events used for intervention and comparators was CheckMate-743. In the model, only treatment-related adverse events ≥ grade 3 adverse events with an incidence ≥ 2% were included (Table 39 of the CS).

ERG comment: The ERG was concerned about the exclusion of many adverse events from the model based on the company's inclusion criteria. In particular, the ERG noted that AE rates used in the model (Table 39 of the CS and later updated in response to clarification question B11[4]) were smaller in the nivolumab + ipilimumab arm compared with the PDC arm, whilst the company's Table 17 of the CS suggests that more AEs occurred in the nivolumab + ipilimumab arm compared with the PDC arm (whether treatment-related or all-cause AEs, any grade or only grade 3-4). In response to clarification question B11[4], the company clarified the source of AEs reported in Table 39 of the CS as Tables 8.5-2 and S.6.2.2 in the CheckMate-743 CSR. The latter Table S.6.2.2 was not made available to the ERG and the AE rates included with ≥ 2% and < 5% incidence used in the model could therefore not be verified.

4.2.8 Health-related quality of life

The utility values were estimated, using EQ-5D-3L (UK scoring algorithm) data obtained in CheckMate-743, for the following health states: PF and progressed disease. These health state utility values were assumed to be treatment dependent.

4.2.8.1 Health-related quality of life data identified in the review

According to the CS, the SLR identified a total of 13 studies that met the eligibility criteria for the review; however, none of the studies evaluated nivolumab + ipilimumab or used the EQ-5D in an appropriate population. Therefore, HRQOL data from CheckMate-743 were used in this submission.

4.2.8.2 Health state utility values

Patient-level utility data from CheckMate-743 were used to derive progression-based utility values for the model. Model fit based on regression models with or without treatment specific utility values were assessed. The analysis showed that treatment had a statistically significant impact on the utility values (P = 0.000). Therefore, treatment dependent health state utilities were selected for the CS base-case. Alternative treatment independent utilities were tested in scenario analyses. A summary of all these utility values is provided in Table 4.3.

Table 4.3: Health state utility values

Health state utility (standard error)	Nivolumab + ipilimumab	Pemetrexed + cisplatin or carboplatin	Difference
CS base-case: treatment dependent			
Progression free	0.737 (0.012)	0.733 (0.012)	0.004
Progressed disease	0.652 (0.014)	0.580 (0.015)	0.072
CS scenario: treatment independent			
Progression free	0.734 (0.008)	0.734 (0.008)	0.000
Progressed disease	0.620 (0.010)	0.620 (0.010)	0.000

4.2.8.3 Disutility values

Specific AE–related disutilities (retrieved from the literature, see CS Table 40) were not incorporated in the CS base-case as it was assumed that the estimated health state utilities already accounted for the AE–related disutilities. In CS scenario 5 AE–related disutilities were of [redacted] and [redacted] were implemented for nivolumab + ipilimumab and PDC respectively.

ERG comment: The main concerns of the ERG relate to: a) the data and methods used to estimate health state utilities and b) the duration of the utility benefits.

a) Details regarding the data and methods used to estimate health state utilities were lacking in the CS. In response to clarification question B12, these details were provided. Mixed models were fitted to the data (using SAS PROC MIXED), to account for repeated EQ5D assessments per subject. According to the company, no strong patterns in the missing data were indicated, and 96.2% (582/605) of all randomised patients had at least one EQ5D utility value. Moreover, the EQ5D utility data was found to be 89% complete (4,899/5,488 EQ5D assessments) with completion rates of above 80% at all on-treatment visits except week 8 and week 108 at 78% (similar in both treatment arms). Given the clarifications provided by the company, the approach used for the CS base-case seems reasonable.
b) The treatment dependent utilities, used in the CS base-case, result in utility benefits for nivolumab + ipilimumab compared to PDC. This is 0.004 and 0.072 for the PF and PD health states. The face validity of the PD utility gain for nivolumab + ipilimumab compared to PDC, as well as its representativeness for UK clinical practice might be an important consideration. Additionally, in the CS base-case, these utility benefits are maintained for the whole duration of the time horizon. The plausibility of this assumption can be debated. Although the company's responses to clarification question B12 were informative and seemed to indicate that there might be a utility benefit even when patients are off treatment (clarification response Tables 26 and 27), the duration/extrapolation of the utility benefit is unclear. Therefore, the ERG base-case adopted the treatment dependent utilities (with the nivolumab + ipilimumab utility benefit) up to three years and treatment independent utilities afterwards (three years was selected given the limited data, only three patients were at risk, at this point).

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition and administration costs, monitoring and management of the disease, end-of-life costs, costs of managing AEs, and costs associated with subsequent therapy.

Unit prices were mostly based on the NHS reference prices[21], British National Formulary (BNF)[22], the Department of Health Drugs and pharmaceutical electronic market information tool (eMIT)[23], and Personal Social Services Research Unit (PSSRU)[24].

4.2.9.1 Resource use and costs data identified in the review

An SLR was conducted to identify costs and resource use in the first-line treatment and ongoing management of patients with MPM as described in Appendix J.[6] The literature search identified no relevant studies reporting the cost and resource use burden associated with MPM's first-line treatment. Due to the limited availability of cost and resource use data in the first-line setting, data irrespective of the line of treatment can also be considered. Three cost analyses were identified, conducted in: Italy, the UK and France[25-27]. These were, however, not used by the company.

4.2.9.2 Treatment costs (with PAS)

A flat nivolumab dosage of 360 mg every three weeks, aligning with the anticipated EMA licence, was used in the base-case analysis. The model includes the option to use the weight-based dose of 3 mg/kg every two weeks that was used in CheckMate-743. The weight-based dose is used in a scenario analysis. Ipilimumab is administered every six weeks at 1 mg/kg, which was in line with CheckMate-743. The CS includes a stopping rule of two years for nivolumab + ipilimumab, which was in line with CheckMate-743 Costs per dose are reported in Table 41 of the CS. There are simple PASs for nivolumab ([redacted]) and ipilimumab ([redacted]) approved by the Department of Health.

The comparator considered was pemetrexed (500 mg/m2 every three weeks for six treatment cycles) + cisplatin (75 mg/m2 every three weeks for four treatment cycles) or carboplatin (550 mg/m2 every three weeks for four treatment cycles). Costs per dose are reported in Table 41 of the CS. In the pemetrexed combination, 33% of patients were assumed to use cisplatin and 67% to use carboplatin, based on CheckMate-743.

The duration of treatment in the model was based on the duration of treatment recorded in CheckMate-743. Given the minimum follow-up was 22.1 months in CheckMate-743 and that the maximum duration of treatment for the nivolumab + ipilimumab arm is 24 months, complete duration of treatment data were available for the pemetrexed + cisplatin or carboplatin arm and data for 98.3% of patients are available for the nivolumab + ipilimumab arm. Thus, use of KM data for duration of treatment would be a viable option instead of parametric survival analyses (described in Appendix K). Both use of KM data and parametric survival analyses were explored, but the former was only used in a scenario and the latter not incorporated in the model. Instead, the company used the mean number of doses reported in CheckMate-743, which were: [redacted] (adjusted from [redacted] to reflect three-weekly doses instead of two-weekly doses) for nivolumab, and [redacted] for ipilimumab. For the PDC arm, the mean number of doses received for pemetrexed, cisplatin, and carboplatin was [redacted], [redacted], and [redacted], respectively. Missed or delayed doses were not corrected for in addition when using this approach, as these were already captured by the approach of using mean doses. Treatment costs were calculated using the mean number of doses and applied in the first model cycle. This approach was chosen over the use of KM data or parametric survival analysis as, according to the company, it *"most accurately captures treatment costs because it accounts for delayed or missed doses and provides values for each treatment within the regimens"*.[4]

Administration costs associated with all treatments are shown in Table 42 of the CS. Nivolumab is administered every three weeks and ipilimumab every six weeks. The cost for delivering complex parenteral chemotherapy is applied when both treatments are administered; the cost for delivering simple parenteral chemotherapy is applied when only nivolumab is administered. Total administration

costs are calculated using the mean number of doses from CheckMate-743 and are also applied in the first model cycle with the company's mean doses approach.

Monitoring costs reflect treatment-specific resource use such as laboratory tests and scans that are required to ensure patients are tolerating the treatment well (Table 43 of the CS). Monitoring costs were modelled for as long as patients stay on treatment, based on the KM data for duration of treatment from CheckMate-743. Monitoring costs were applied to the proportion of patients on treatment in each model cycle using separate KM curves for nivolumab + ipilimumab and for pemetrexed + cisplatin or carboplatin.

4.2.9.3 Subsequent treatment costs

According to the company, on failure with first-line treatment of nivolumab + ipilimumab or pemetrexed + cisplatin or carboplatin (i.e. on entry to the PD health state), proportions of 44.22% of patients on nivolumab + ipilimumab and 40.73% of patients in the PDC arm were modelled to go on to a subsequent treatment. The distribution of subsequent therapies received by initial treatment was based on CheckMate-743. Four subsequent treatment strategies were omitted because of low usage (< 1%). The median duration of 1.7 months assumed for all subsequent therapies (irrespective of therapy or treatment arm) was based on the publication by Waterhouse et al [28] (both distribution and duration of subsequent treatments are presented in Table 44 of the CS). Dosing details of all subsequent treatments are presented in Table 45 and administration costs in Table 46 of the CS.

4.2.9.4 Health state costs

Health state costs related to the PF health state (Table 47 of the CS), the progressed disease health state (Table 48 of the CS), and the end of life/terminal care cost health state (Table 49 of the CS). The weekly disease management costs for the PF state includes as outpatient visits chest radiography, CT scans (chest), CT scans (other), and electrocardiograms and the frequencies for these were obtained from TA531[29], amounting to a total cost per week of £42.60. For the PD state, weekly costs in addition include GP home visits, and therapist visits, with frequencies (every other week for both GP and therapist visits) also based on TA531[29], amounting to a total cost per week of £107.85. End of life/terminal care costs of £5,018.27 were applied as a one-off cost upon entering the death state. These costs included community nurse visits, GP home visits, Macmillan nurse, drugs and equipment, terminal care in hospital and terminal care in hospice, which frequencies obtained from TA531.

4.2.9.5 Event costs

Cost of treatment-related AEs (grade ≥ 3 AEs with an incidence rate of ≥ 2%) are shown in Table 4.4. Combined with the incidence of AEs in both treatment arms shown in Table 39 of the CS, this resulted in AE costs of £106.13 for nivolumab + ipilimumab, and £726.23 for the PDC arm, which are applied as a one-off in the first model cycle.

Table 4.4: Costs per weekly cycle

	Nivolumab + ipilimumab arm		PDC arm	
Treatment cost (£)	Nivolumab 360 mg Q3W, up to 2 years (company base-case)	[redacted]	Pemetrexed 500 mg/m^2 Q3W for 6 treatment cycles§	300.00
	Nivolumab 3 mg/kg Q2W, up to 2 years (company scenario)§	[redacted]	Cisplatin 75 mg/m^2 Q3W for 4 treatment cycles§	1.89

	Nivolumab + ipilimumab arm		PDC arm	
	Ipilimumab 1 mg/kg Q6W, up to 2 years§	[redacted]	Carboplatin 550 mg/m^2 Q3W for 4 treatment cycles§	7.91
Treatment administration cost (£)	Nivolumab + ipilimumab*	101.12	Pemetrexed + cisplatin or carboplatin**	88.09
Monitoring cost (£)	CS Table 43	50.33	CS Table 43	50.02
Subsequent treatment cost (£)	CS Tables 44 and 45	[redacted]	CS Tables 44 and 45	[redacted]
Health state cost (£)	PF state	42.60	PF state	42.60
	PD state	107.85	PD state	107.85
	End of life / terminal care	5,018.27	End of life / terminal care	5,018.27
Adverse event cost (£)	CS Table 50	106.13	CS Table 50	726.28

CS = company submission; PD = progressed disease; PDC = platinum-based doublet chemotherapy; PF = progression-free
§Mean patient characteristics used for calculations of weekly drug costs
*Based on company's mean doses approach, calculated over median TTD of approximately 24 weeks
**Based on company's mean doses approach, calculated over median TTD of approximately 15 weeks

ERG comment: The main concerns of the ERG relate to: a) proportional use of cisplatin versus carboplatin in the comparator arm; b) the approach to estimating treatment duration; c) the approach to including subsequent treatments in the analysis; d) costs related to AEs.

a) The ERG was concerned that the proportions to which the comparator included carboplatin versus cisplatin were unclear. The company clarified this and also performed a minor correction to the model: carboplatin was used by 66% of patients and cisplatin by 34% of patients in CheckMate-743. Regarding the generalisability of these proportions to UK clinical practice, the company clarified in response to clarification question B14[3] that "*Data from the EU cross-sectional study for the cohort of 248 UK patients suggest a similar proportion of carboplatin and cisplatin use. In the UK,* [redacted] *[10]. The proportions used in the model are more similar to estimates from The UK National Mesothelioma Audit 2020 in which pemetrexed with carboplatin was the most common regimen used (48%), followed by pemetrexed with cisplatin (20%), in patients who received chemotherapy."*[9] However, as noted in the ERG critique in Section 2 of this report, these numbers suggest some variation in the proportion of use of carboplatin versus cisplatin. Due to the low weekly cost of carboplatin and cisplatin, the magnitude of proportional use has a minor impact on cost effectiveness outcomes, as demonstrated by the company's scenario assuming an equal split between carboplatin and cisplatin use, which increased the ICER by £23 per QALY gained.
b) The use of mean number of doses to estimate treatment duration may introduce bias because this method does not take account of right-censoring[30]. According to Appendix N, the health economic experts agreed that *"that the CM-743 time-to-treatment discontinuation K-M curves were the best available evidence to inform treatment duration"*[6]. The ERG agrees with the experts, but also considers that parametric survival analysis on this evidence may potentially

be preferred, using dose intensity to reflect missed and delayed doses, and reflecting the stopping rule for nivolumab + ipilimumab by discontinuing all patients still on treatment at 24 months. The ERG requested this analysis from the company at clarification stage, but the company did not provide this analysis. In response to question B13 the company claimed that UK clinical experts considered the mean number of doses approach the most appropriate[3]. However, this was not supported by a reference (the company points to page 100 of their report, however this statement is not made there). The company's rationale for maintaining the mean number of doses approach is that the KM data, or parametric distributions do not account for missed or delayed doses. However, this can be addressed by using dose intensity as observed in CheckMate-743, as was proposed by the ERG in the clarification letter and is not considered by the ERG as a strong argument for not performing this analysis. In terms of the bias that might be introduced by using the mean number of doses approach, the company states that because the data are mature (minimum follow-up time is 22.1 months, the median is 29.7 months and the stopping rule for treatment is at 24 months), right-censoring would have minimal impact on the final estimates of doses received. The company also committed to providing updated duration of treatment data once these are available. Whilst the ERG considers the company's argument plausible, it would prefer to see the impact explored in scenario analysis using parametric survival models fitted to the time-to-treatment discontinuation KM data and using dose intensity. The mean dose intensity for each treatment was not made available by the company, but Table 6.1-1 of the CheckMate-743 CSR indicated dose intensity of around [redacted] for all treatments[7]. Because the company did not provide parametric survival analysis for TTD and mean dose intensity estimates were not available, the ERG used TTD KM estimates and 100% dose intensity for all treatments in a scenario. As far as generalisability is concerned, TTD KM estimates for the PDC arm were compared with available data for SACT from the CAS registry of patients with unresectable MPM in Figure 13 in the CQ response and showed that median treatment duration was [redacted] in the CAS registry compared with CheckMate-743[3]. No potential reasons for this discrepancy were provided.

c) There is remaining uncertainty about the modelling of subsequent treatments. These are only used by a proportion of patients in the PD state: 44.22% in the nivolumab + ipilimumab arm and 40.73% in the PDC arm as per CheckMate-743. The company confirmed in response to clarification question B15 that these proportions were aligned with clinical expectations according to clinical experts consulted during the development of the economic model, but the company also acknowledged that these proportions could be higher or lower in clinical practice.
Subsequent treatments used are in line with CheckMate-743 but their use may not be in line with UK clinical practice. According to the company's response to question B15, there is no standard second-line therapy in MPM used in NHS clinical practice and this was also confirmed by UK clinical experts. For example, nivolumab + ipilimumab will only be used in the first-line setting, not in second-line. Re-treatment or re-challenge with nivolumab + ipilimumab is also not supported by any data currently, according to the company. Re-treatment with pemetrexed + cisplatin/carboplatin was shown by the company to be in line with UK clinical practice.
Subsequent treatment duration of 1.7 months regardless of the subsequent treatment received and prior treatment allocation is considered by the ERG unlikely to be a good reflection of clinical practice. This was based on a poster by Waterhouse et al[28], in which the mix of second-line treatments differed from that in CheckMate-743 and the model. There was large variation in subsequent treatment duration (interquartile range of 1 – 11.90 in Waterhouse et al), and the differences may partly be driven by the type of subsequent treatment or prior treatment. First,

treatment duration may be longer with immunotherapies than with chemotherapies. Second, treatment duration may differ by initial treatment allocation, as post-progression survival appears to be longer in the modelled nivolumab + ipilimumab arm compared with the PDC arm. The company stated that the assumption of equal subsequent treatment duration would be conservative, given that immunotherapies would be expected to have a longer duration of treatment compared with chemotherapies and there was a higher proportion of immunotherapies in the PDC arm. However, the ERG considers that uncertainty remains about subsequent treatment duration and that it would ideally be able to implement differential subsequent treatment durations for each model arm (currently not enabled in the model), possibly based on data from CheckMate-743 once these are available, or expert opinion. The company provided scenario analyses to explore the impact of different assumptions surrounding subsequent treatments in Table 30 of the clarification response[3]. These scenarios, for example increasing subsequent treatment duration in both arms, resulted in only relatively small changes to the base-case ICER. In addition, the ERG performed a scenario setting subsequent treatment costs in the nivolumab + ipilimumab arm equal to the subsequent costs in the PDC arm and increasing treatment duration in both arms to three months. The impact of this was still minor.

d) As pointed out in Section 4.2.7, there may be selection bias in the included AEs which may result in an over-estimation of the incremental AE costs for the PDC arm versus the nivolumab arm. The company did not provide cost effectiveness analyses with all-causality (treatment-emergent) AEs instead of only treatment-related AEs, and the restriction on the incidence changed to 1% as requested by the ERG in the clarification letter. Equal AE rates for both treatment arms (using currently included AEs) would result in an increase in the ICER of slightly less than £1,000 per QALY gained and it should be noted that it only affects costs. Despite this not being a very impactful issue the ERG considers that the impact of AEs on the two treatment arms is currently likely mis-represented in the model.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

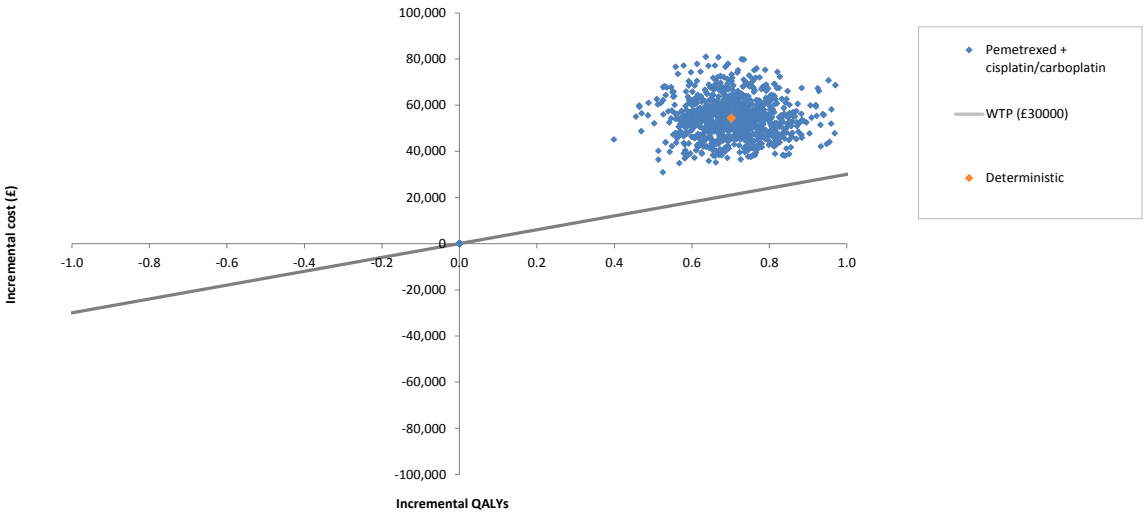
The CS base-case cost effectiveness results (probabilistic) indicated that nivolumab + ipilimumab is both more effective (incremental QALYs of 0.706) and more costly (additional costs of £55,423) than PDC amounting to an ICER of £77,127 per QALY gained (Table 5.1). Moreover, the 95% percentiles for the probabilistic incremental costs and QALYs were (£39,156 - £72,154) and (0.543 - 0.882) respectively (Figure 5.1). The probabilities of nivolumab + ipilimumab being cost effective, at thresholds of £20,000, £30,000 and £50,000 per QALY gained, compared to PDC are 0%, 0% and 1% respectively.

Overall, nivolumab + ipilimumab is modelled to affect QALYs in the company base case by:

- Increased mean PFS (undiscounted time in the PF health state: [redacted] months) and mean OS (undiscounted survival: [redacted] months) compared with PDC.
- Increased health state utility values for the PF (0.74 vs 0.73) and PD (0.65 vs 0.58) health states compared with PDC.
- The PFS, OS and health state utility benefits are maintained for the whole duration of the time horizon (i.e. no waning of these treatment benefits).

These effects combined result in the majority (55%) of the QALY gains (58% of the undiscounted LYs) being accumulated in the pre-progression state (CS Appendix L Tables 49 and 50). The majority (92%) of the additional costs are also accumulated due to increased drug acquisition costs followed by increased PD (4%) and PF (2%) health state costs (CS Appendix L Table 51).

Figure 5.1: CS base-case cost effectiveness plane



Source: Economic model

Table 5.1: CS base-case results

	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£)
Deterministic							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	54,397	0.916	0.702	77,502
Probabilistic (1,000 iterations)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	55,423	0.921	0.706	77,127
Source: CS Table 55[2] and economic model							

5.1.1 Company's subgroup analyses

No subgroup analyses were performed.

ERG comment: The main concerns of the ERG relate to: a) minor errors in the original CS base-case and b) extent and plausibility of the observed gains accumulated beyond the observed data period; c) not exploring cost effectiveness for subgroups listed in the scope.

a) In the clarification responses, the company started section B with the highlighting of two errors identified in the economic model used to calculate the CS base-case. These errors related to:
    a. One drug-related AE occurring in ≥ 2% of patients was omitted (see response to question B11, part a)
    b. The proportions of cisplatin and carboplatin use in combination with pemetrexed were incorrect (see response to question B14, part a)

   The company corrected these errors in their revised base-case. Compared with the original CS base-case, these corrections did not impact the estimated effectiveness (LY/QALYs), the company's revised base-case (deterministic) only slightly increased the estimated (incremental) costs as well as the ICER (increased from £77,502 to £77,531). Probabilistic results for the revised company base-case were not provided.
b) In clarification question B17, the ERG requested the company to provide a comparison of the observed survival as well as progression free survival for instance using restricted mean survival time (RMST) and the undiscounted LY as well as undiscounted progression free LY (PFLY) and elaborate on the plausibility of the differences. Unfortunately, the company stated that RMST was not reported in CheckMate-743. The RMST can be easily calculated from the KM data provided in the economic model. Therefore, the ERG calculated the RMST for LY as well as PFLY using different truncation points (Table 5.2). Based on these calculations it can be derived that the proportion of (PF)LY accumulated beyond the observed data is substantially larger for nivolumab + ipilimumab than for PDC. Moreover, considering the increments, approximately [redacted] of the LYs are gained beyond the observed data period for nivolumab + ipilimumab compared with PDC while this is even larger (approximately [redacted] for PFLY. While the company's response to clarification questions B5 and B8 give some indication about the plausibility of the long-term extrapolations, the findings presented in Table 5.2 indicate that the large majority of gains are accumulated beyond the observed data period and hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted (as requested but not provided in the company's response to clarification question B17). This includes verifying the plausibility of the partitioned survival model extrapolations (see Section 4.2.2). Additionally, this highlights that the generated differences beyond the observed data period are a key issue while the estimated (PF)LY for the observed data period (i.e. whether to use KM data due to suboptimal fit in the observed data period) might have less priority.
c) The NICE scope mentioned subgroups based on histologic subtype (epithelioid, sarcomatoid, biphasic) and level of programmed death-ligand 1 (PD-L1) expression. These subgroups were not considered in the cost effectiveness sections of the CS despite these were prespecified subgroup analysis in CheckMate-743 (CS Table 7) and the relative effectiveness might differ between these subgroups (CS Figure 23 regarding OS hazard ratios per subgroup; tests for interactions were unfortunately not provided by the company despite requested in clarification question A13, while for PFS Section 3.2.5 suggests qualitative interactions regarding relative treatment effectiveness for these subgroups). Therefore, it might be informative to consider

subgroups specific cost effectiveness analyses. See also section 3.2.5 and 4.2.3 for further details.

Table 5.2: CS base-case comparing observed and estimated undiscounted (PF)LYs

	Observed	Modelled	
	Restricted mean survival time (RMST)[a]	**Estimated (lifetime time horizon)**	**Proportion beyond observed data[a]**
OS - RMST period / truncation point: 30 months (selected based on patients at risk Table)			
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]
Increment[a]	[redacted]	[redacted]	[redacted]
OS - RMST period / truncation point: 22 months (break point for piecewise approach[b])			
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]
Increment[a]	[redacted]	[redacted]	[redacted]
OS - RMST period / truncation point: [redacted] months (latest KM data point: [redacted] months)			
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]
Increment[a]	[redacted]	[redacted]	[redacted]
PFS - RMST period / truncation point: 30 months (selected consistently with OS)			
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]
Increment[a]	[redacted]	[redacted]	[redacted]
PFS - RMST period / truncation point: 22 months (break point for piecewise approach[b])			
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]
Increment[a]	[redacted]	[redacted]	[redacted]
PFS - RMST period / truncation point: [redacted] months (latest KM data point: [redacted] months)			
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]
Increment[a]	[redacted]	[redacted]	[redacted]

Source: economic model

[a]Calculated by the ERG (based on information on the "KM Data Store" worksheet), the estimated numbers might be subject to rounding errors

[b]The company justified the 22 months break point by stating that it was the approximate minimum patient follow-up at the database lock of CheckMate-743, and most censoring in the OS data in both treatment arms occurred after this point

5.2 Company's sensitivity and scenario analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses.

The parameters that have the greatest effect on the ICER (based on the company's sensitivity analyses illustrated in CS Figure 43) are:

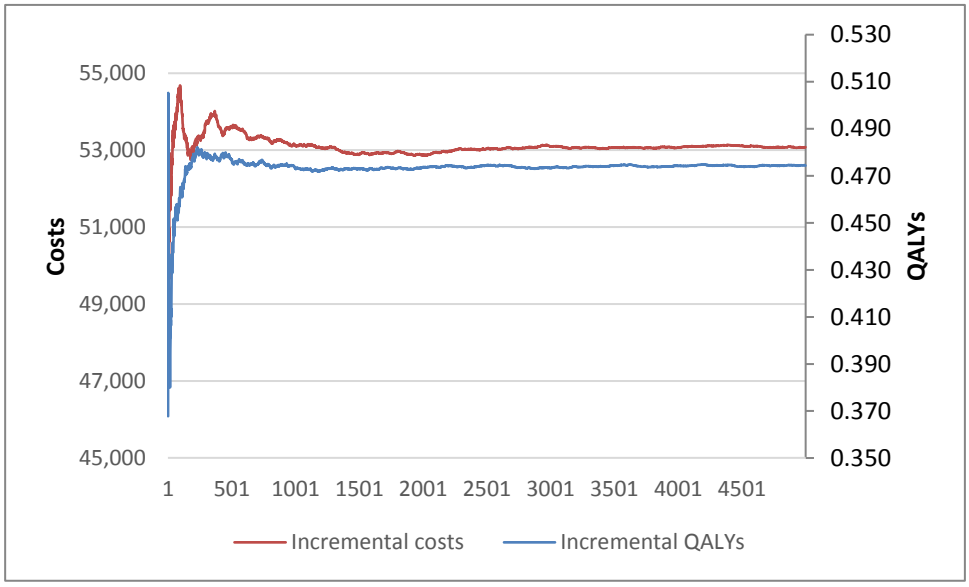
- PF and PD health state utility values for nivolumab + ipilimumab
- PF and PD health state utility values for PDC
- Discount rates for outcomes and costs
- Nivolumab and ipilimumab dosing
- Pemetrexed dosing
- Cohort starting age

Consistently, modelling assumptions that relate to these parameters likely have the greatest effect on the ICER. This is illustrated by the following CS scenarios that have a substantial impact on the ICER:

- CS scenarios 1-3: estimating OS using an alternative approach
- CS scenario 5: using treatment independent utility values
- CS scenario 4: estimating PFS using an alternative approach
- CS scenario 6: using nivolumab weight-based dosing

ERG comment: The main concern of the ERG relates to the number of PSA iterations being insufficient. The convergence plots in Figure 5.2 show that incremental costs and QALYs were not yet completely stable at 1,000 iterations in the ERG base-case. This might particularly hamper the comparison/interpretation of scenarios with very similar (incremental) results. It should also be noted that in scenarios using TTD estimates or KM estimates (in the piecewise approach), these should be included in the PSA, but it appears as if they are not (given these are not included in the parameter sheet).

Figure 5.2: PSA convergence plot for ERG base-case



5.3 Model validation and face validity check

5.3.1 Face validity assessment

During the development of the economic model, external clinical and health economic experts were consulted to ensure an appropriate approach was taken and that the model had clinical validity. Three advisory boards including UK clinical and HTA experts were held for this purpose.

5.3.2 Technical verification

The company did not provide detail on the technical verification of their model.

5.3.3 Comparisons with other technology appraisals

No comparisons with other technology appraisals were provided.

5.3.4 Comparison with external data

The company undertook comparisons between their modelled OS extrapolations, CheckMate-743 OS data (used to develop this model) and OS data from the MAPS dataset (not used to develop the model).

ERG comment: The main concerns of the ERG relate to: a) internal validity efforts, and b) lack of cross-validation.

a) The internal validity or technical verification was not detailed by the company, but in response to clarification question B18, the company clarified that *"the model was quality controlled and all calculations and data were checked by an independent researcher"*[3]. The ERG also requested that a checklist be filled in, such as the TECH-VER checklist[31], but the company did not provide this. Although the internal validity was not fully demonstrated, the ERG was able to reproduce life year gains, QALY gains and costs of the company's base-case.
b) No cross-validation with other technology appraisals was provided. In response to clarification question B19, the company stated that TA135 was not suitable for cross-validation but did not explore potential cross-validation with other appraisals. The ERG acknowledges that cross-validation with other appraisals would be limited since there are no published appraisals in MPM to date (apart from TA135).

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020[32]:

- Transparency (e.g. lack of clarity in presentation, description, or justification)
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g. particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g. there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e. whether additional clarifications, evidence and/ or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the ERG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this ERG report, the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016)[33]:

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

6.1.1 ERG base-case

Adjustments made by the ERG, to derive the ERG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the ERG base-case. The ERG did not identify any errors or violations and all adjustments pertained to matters of judgement.

6.1.1.1 Matters of judgement

1. The use of piecewise KM estimates for OS extrapolation (Section 4.2.6)
   ERG adjustment: do not use the piecewise approach
2. The use of log-logistic and exponential distributions for OS in nivolumab + ipilimumab and PDC arms respectively (Section 4.2.6)
   ERG adjustment: use log-logistic distributions for OS in both treatment arms
3. Assumption that treatment effect will persist through lifetime (Section 4.2.6)
   ERG adjustment: implement treatment waning from five years onwards by adjusting the nivolumab + ipilimumab OS and PFS hazards to align with those of the PDC arm after this time point
4. Assumption that treatment effect on utilities will persist throughout lifetime (Section 4.2.8)

ERG adjustment: change to treatment independent utilities at three years

6.1.2 ERG exploratory scenario analyses

The ERG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the ERG base-case.

6.1.2.1 Exploratory scenario analyses

1. Uncertainty about PFS (Section 4.2.6)
   a) ERG adjustment: Use log-logistic distributions for both arms
   b) ERG adjustment: Use generalised gamma distributions for both arms
2. Likely selection bias in AEs (Section 4.2.7)
   ERG adjustment: set AE rates equal in both treatment arms
3. Potentially biased approach to time-on-treatment estimation (Section 4.2.9)
   ERG adjustment: use TTD KM estimates with 100% dose intensity
4. Likely bias in subsequent treatment duration estimate (Section 4.2.9)
   ERG adjustment: set equal nivolumab + ipilimumab arm subsequent treatment costs to PDC arm subsequent treatment costs and increase subsequent treatment duration for both to 3 months

6.1.3 ERG subgroup analyses

No subgroup analyses were performed by the ERG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue pertaining to cost effectiveness (See Section 1)	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base-case
6) No state transition model provided to validate the partitioned survival analysis model	4.2.2	Methods	State transition model	+/-	No
7) No subgroup analysis provided	4.2.3	Methods	Subgroup analysis	+/-	No
8) Two-year stopping rule may not be observed in CheckMate-743 (although included in study protocol)	4.2.4	Indirectness	Correct for this if necessary (proportion of patients not adhering to stopping rule in cost estimation)	Could be +, if applicable	No
9) Treatment effectiveness and extrapolation of OS and PFS for nivolumab + ipilimumab highly uncertain due to immature data, limited long-term validation	4.2.6	Methods, unavailability	Alternative approaches for estimating PFS and OS as well as assumptions related to treatment waning	+/-	Partly, data immaturity cannot be currently resolved
10) Duration of treatment effect on HRQoL uncertain	4.2.8	Methods, unavailability	Treatment independent utilities from certain time point	+	Partly, explore appropriate time point
11) Estimation of time on treatment potentially biased	4.2.9	Methods	Use TTD KM estimates and parametric survival analysis and dose intensity	+	Partly, dose intensity adjustment needed
12) Duration of subsequent treatments potentially biased, remaining uncertainty about subsequent treatment use	4.2.9	Imprecision, indirectness	Longer subsequent treatment duration in both arms and set costs equal	+	Partly, differential implementation of subsequent treatment duration per arm needed
13) Selection bias in AE rates and therefore likely bias in AE associated costs	4.2.9	Indirectness	Set AE rates equal, or preferable incorporate all cause AEs	+	Partly, enable all cause AEs

Key issue pertaining to cost effectiveness (See Section 1)	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base-case
14) Large proportion of (PF)LY accumulated beyond the observed data	5.1	Unavailability	Using CheckMate-743 data with additional follow-up data.	+/-	No

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator

AE = adverse events; ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; KM = Kaplan-Meier; LY = life years; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In Section 6.1 the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the ERG base-case. The analyses numbers in Tables 6.2 and 6.3 correspond to the numbers reported in Section 6.1. The submitted model file contains technical details on the analyses performed by the ERG (e.g. the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: ERG base-case (deterministic unless indicated)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company's corrected base-case							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	54,417	0.916	0.702	77,531
Matter of judgement 1: do not use piecewise approach (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	54,579	0.943	0.719	75,867
Matter of judgement 2: use log-logistic distributions for OS in both treatment arms (using piecewise) (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,269	0.700	0.576	92,413
Matter of judgement 3: implement treatment waning from 5 years onwards (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	52,988	0.540	0.443	119,543
Matter of judgement 4: change to treatment-independent utilities from 3 years onwards (key issue 10)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	54,417	0.916	0.678	80,206
ERG base-case (Changes 1-4)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,327	0.617	0.476	112,005

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ERG base-case probabilistic (5,000 runs)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,076	0.612	0.474	111,898

Table 6.3: Deterministic scenario analyses (conditional on ERG base-case)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ERG base-case							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,327	0.617	0.476	112,005
Scenario 1a: PFS log-logistic distribution for both arms (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,861	0.617	0.460	117,179
Scenario 1b: PFS generalised gamma distribution for both arms (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,602	0.617	0.467	114,786
Scenario 2: set AE rates equal in both treatment arms (key issue 13)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,927	0.617	0.476	113,267
Scenario 3: use TTD KM estimates with 100% dose intensity (key issue 11)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	59,726	0.617	0.476	125,446
Scenario 4: set equal nivol + ipi arm subsequent treatment costs to PDC & increase treatment duration to 3 months (key issue 12)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,812	0.617	0.476	113,024

Table 6.4: Probabilistic scenario analyses (conditional on ERG base-case, 1,000 iterations unless stated otherwise)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company base-case							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	54,396	0.926	0.710	76,633
ERG base-case (5,000 iterations)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,076	0.612	0.474	111,898
Scenario 1a: PFS log-logistic distribution for both arms (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,981	0.618	0.460	117,281
Scenario 1b: PFS generalised gamma distribution for both arms (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,147	0.611	0.464	114,466

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Scenario 2: set AE rates equal in both treatment arms (key issue 13)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,505	0.611	0.475	112,539
Scenario 3: use TTD KM estimates with 100% dose intensity (key issue 11)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	59,693	0.617	0.477	125,139
Scenario 4: set equal nivol + ipi arm subsequent treatment costs to PDC & increase treatment duration to 3 months (key issue 12)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,981	0.614	0.475	113,612

6.3 ERG's preferred assumptions

The estimated ERG base-case ICER (probabilistic), based on the ERG preferred assumptions highlighted in Section 6.1, was £111,898 per QALY gained. The probabilistic ERG base-case analyses indicated cost effectiveness probabilities of 0%, 0% and 0% at willingness to pay thresholds of £20,000, £30,000 and £50,000 per QALY gained. The most influential adjustments were implementing treatment waning from five years onwards and using the log-logistic distribution for estimating OS in the PDC arm. The ICER increased most in the scenario analysis using TTD estimates with 100% dose intensity instead of the number of mean doses approach. Since dose intensity was likely lower in the trial, this may be regarded as a the upper bound of the ICER using alternative scenarios on time on treatment.

6.4 Conclusions of the cost effectiveness section

The company's cost effectiveness model was well built and complied with the NICE reference case. The main critique points are modelling choices and assumptions. The overarching challenge was the immaturity of the data from CheckMate-743, which results in the ICER being very uncertain. The company's approach of using a PSM was questioned, especially given that a large proportion of life years and QALYs gains could be attributed to the time period beyond available trial data. The most influential issue was the extrapolation of OS. The ERG considered the company's piecewise approach not to offer any improvements over conventional survival analysis and replaced it by conventional survival analysis in the ERG base-case. Given current evidence, the ERG also questioned the company's choice of distributions (log-logistic and exponential) and preferred the log-logistic distribution in both arms. The ERG furthermore questioned the company's implicit assumption of a lifelong treatment effect (OS and PFS) and relaxed this by implementing treatment waning from five years onwards in the ERG base-case, which had a significant impact on the ICER. The ERG also explored the impact of different PFS distributions in scenarios, which was smaller compared with OS modifications. AEs may be mis-represented in the cost effectiveness analysis model because of the company's applied selection criteria, which could result in underestimation of AE-related costs in the model. The impact of this on cost effectiveness results is likely small. In terms of HRQoL, the main uncertainty related to whether the treatment effect on HRQoL was lifelong and the ERG relaxed this assumption in the ERG base-case. The ERG questioned the method of using number of mean doses for estimating treatment duration, which may be biased due to right-censoring. Even though the company highlighted that the data were mature and right-censoring therefore unlikely to be a significant problem, the ERG considered that since treatment duration was a key driver of the model, the impact of using parametric survival analysis using TTD data should be explored. Subsequent treatments and their treatment duration were also subject to uncertainty and may warrant further investigation, even though the impact on cost effectiveness may be relatively small. No subgroup analyses were provided, but the ERG considered that cost effectiveness may vary by subgroup.

The company's corrected deterministic ICER was £77,531 per QALY gained and no corrected probabilistic ICER was presented. The ERG's replication of the company base-case probabilistic analysis resulted in an ICER of £76,633 per QALY gained. The estimated ERG base-case ICER (probabilistic), based on the ERG preferred assumptions highlighted in Section 6.1, was £111,898 per QALY gained. The probabilistic ERG base-case analyses indicated cost effectiveness probabilities of 0% and 0% at willingness to pay thresholds of £30,000 and £50,000 per QALY gained. The most influential adjustments were implementing treatment waning from five years onwards and using the log-logistic distribution for estimating OS in the PDC arm. The ICER increased most in the scenario analysis using TTD estimated with 100% dose intensity instead of the mean doses approach. Since dose

intensity was likely lower in the trial, this may be regarded as a the upper bound of the ICER using alternative scenarios on time on treatment.

There is large remaining uncertainty about the effectiveness and relative effectiveness of nivolumab + ipilimumab versus PDC, which can be at least partly resolved with future analyses of CheckMate-743 data. In view of the immaturity of the CheckMate-743 study it was not possible for the ERG to quantify all uncertainty now. Further data cuts could potentially result in additional survival gains for the nivolumab + ipilimumab arm. However, it is currently questionable whether nivolumab + ipilimumab can be cost effective compared to PDC.

7. END OF LIFE

The company claim that the end of life criteria are fulfilled:[2]

- Most patients die less than two years after diagnosis, with a median survival of 13 months in unresectable patients with MPM treated with SACT.[34]
- Interim results from CheckMate-743 show a median 4-month survival benefit with nivolumab + ipilimumab versus PDC, with a median OS follow-up of 29.7 months.

ERG comment: As reported in Section 3.2.4.1, the ERG notes also that PDC had a median OS of 14.1 months (95% CI: 12.4 to 16.2 months), which would be consistent with a survival that was lower than two years. In additions, the company's base-case model supports this as it results in an undiscounted mean OS of 1.7 years (Table 5.2). However, the ERG base-case indicates possible undiscounted mean OS of exactly two years. The ERG can also verify the increase in survival of four months given that those treated with nivolumab + ipilimumab were noted to have a median OS of 18.1 months (95% CI: 16.8 to 21.4 months). The company's and ERG's base-case analyses support the survival gain of > 3 months.

8. REFERENCES

[1] Baas P, Daumont MJ, Lacoin L, Penrod J, Carroll R, Tanna N. Treatment patterns and outcomes in malignant pleural mesothelioma in England: a nationwide CAS registry analysis from the I-O Optimise initiative. Poster presented at European Society for Medical Oncology (ESMO) Virtual Congress; 19-21 September 2020.

[2] Bristol-Myers Squibb. *Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]: submission to National Institute of Health and Care Excellence. Single technology appraisal (STA)*. Uxbridge: Bristol-Myers Squibb, 2020. 129p.

[3] National Institute for Health and Care Excellence. *Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]: clarification letter*. London: NICE, 2021. 21p.

[4] Bristol-Myers Squibb. *Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]: response to request for clarification from the ERG*. Uxbridge: Bristol-Myers Squibb, 2021. 85p.

[5] Tsao AS, Baas P, Nowak AK, Zalcman G, Fujimoto N, Peters S, et al. Evaluation of flat dosing for nivolumab + ipilimumab in first-line unresectable malignant pleural mesothelioma: CheckMate 743. Presented at ESMO Immuno-Oncology Virtual Congress 2020; 9-12 December 2020.

[6] Bristol-Myers Squibb. *Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]: document C [Appendices]. Submission to National Institute for Health and Care Excellence. Single technology appraisal (STA)*. Uxbridge: Bristol-Myers Squibb, 2020. 129p.

[7] Bristol-Myers Squibb. *Nivolumab + ipilimumab: final clinical study report for study CA209743. A phase III, randomized, open label trial of nivolumab in combination with ipilimumab versus pemetrexed with cisplatin or carboplatin as first line therapy in unresectable pleural mesothelioma*. Lawrenceville (NJ): Bristol-Myers Squibb, 3 August 2020. 152p.

[8] Woolhouse I, Bishop L, Darlison L, De Fonseka D, Edey A, Edwards J, et al. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. *Thorax* 2018;73(Suppl 1):i1-i30.

[9] Royal College of Physicians. *National mesothelioma audit report 2020 (for the audit period 2016-18) [Internet]*. London: RCP, May, 2020 [accessed 2.2.21]. 27p. Available from: https://www.rcplondon.ac.uk/file/21631/download

[10] Moore AB, Hart K, McDonald L, McKenna M, Daumont MJ. *Malignant pleural mesothelioma: treatment patterns and humanist burden of disease in Europe [manuscript in prepration]*, 2021

[11] Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. *Cochrane handbook for systematic reviews of interventions version 6.0 (updated July 2019) [Internet]*: Cochrane, 2019 [accessed 6.7.20] Available from: https://training.cochrane.org/handbook

[12] National Institute for Health and Care Excellence. *Single Technology Appraisal: specification for manufacturer/sponsor submission of evidence [Internet]*. London: NICE, 2012 [accessed ??]. 76p. Available from: http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Specification-for-manufacturer-sponsor-submission-of-evidence-June-2012.doc

[13] Baas P. First-line nivolumab + ipilimumab vs chemotherapy in unresectable malignant pleural mesothelioma: CheckMate 743. Presented at International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC); 8 August 2020.

[14] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [accessed 23.3.11] Available from: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm

[15] Woods B, Sideris E, Palmer S, Latimer N, M. S. *NICE DSU technical support document 19. Partitioned survival analysis for decision modelling in health care: a critical review [Internet]*. Sheffield: University of Sheffield, 2017 [accessed 2.2.21]. 72p. Available from: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf

[16] Burnham K, Anderson D. *Model selection and multimodel inference: a practical information-theoretic approach*. 2nd ed. New York: Springer, 2004.

[17] Raftery AE. Bayesian model selection in social research. *Sociol Methodol* 1995;25:111-63.

[18] Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2016;387(10026):1405-1414.

[19] Antonia SJ, Borghaei H, Ramalingam SS, Horn L, De Castro Carpeno J, Pluzanski A, et al. Four-year survival with nivolumab in patients with previously treated advanced non-small-cell lung cancer: a pooled analysis. *Lancet Oncol* 2019;20(10):1395-408.

[20] National Institute for Health and Care Excellence. Nivolumab for treated squamous cell carcinoma for the head and nedk after platinum-based chemotherapy (CDF Review TA490) [ID1585] [Internet]. London: NICE, 2021 [accessed 9.3.21]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10538/documents

[21] NHS Improvement. 2018/2019 National cost collection data [Internet]. Leeds: NHS Digital, 2020 [accessed 2.2.21]. Available from: https://improvement.nhs.uk/resources/national-cost-collection/

[22] National Institute for Health and Care Excellence. BNF [Internet]. London: NICE, 2021 [accessed 9.2.21]. Available from: https://bnf.nice.org.uk/

[23] Department of Health and Social Care. *Drugs and pharmaceutical electronic market information tool (eMIT) [Internet: Excel spreadsheet]*. Leeds: Department of Health and Social Care, 4 March, 2020 [accessed 2.2.21] Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit

[24] Curtis LAB, A. *Unit Costs of Health and Social Care 2019 [Internet]*. Canterbury: Personal Social Services Research Unit, University of Kent, 2019 [accessed 2.2.21]. 184p. Available from: https://kar.kent.ac.uk/79286/11/UCFinalFeb20.pdf

[25] Ippoliti R, Falavigna G, Grosso F, Maconi A, Randi L, Numico G. The economic impact of clinical research in an Italian public hospital: the malignant pleural mesothelioma case study. *International journal of health policy and management* 2018;7(8):728-737.

[26] Verma V, Ahern CA, Berlind CG, Lindsay WD, Grover S, Culligan MJ, et al. Facility volume and postoperative outcomes for malignant pleural mesothelioma: a National Cancer Data Base analysis. *Lung Cancer* 2018;120:7-13.

[27] Chouaid C, Assié JB, Andujar P, Blein C, Tournier C, Vainchtock A, et al. Determinants of malignant pleural mesothelioma survival and burden of disease in France: a national cohort analysis. *Cancer Med* 2018;7(4):1102-1109.

[28] Waterhouse D, Nwokeji E, Boyd M, Penrod JR, Espirito J, Robert NJ, et al. Treatment patterns and outcomes of advanced malignant pleural mesothelioma (MPM) patients in a community practice setting. Poster presented at the International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer; 7-10 September 2019; Barcelona, Spain

[29] National Institute for Health and Care Excellence. *Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer [TA531]. Committee papers [Internet]*. London: NICE, 2018 [accessed 2.2.21]. 305p. Available from: https://www.nice.org.uk/guidance/ta531/documents/committee-papers

[30] Wijeysundera HC, Wang X, Tomlinson G, Ko DT, Krahn MD. Techniques for estimating health care costs with censored data: an overview for the health services researcher. *ClinicoEconomics and outcomes research: CEOR* 2012;4:145.

[31] Büyükkaramikli NC, Rutten-van Mölken M, Severens JL, Al M. TECH-VER: A verification checklist to reduce errors in models and improve their credibility. *Pharmacoeconomics* 2019;37(11):1391-408.

[32] Grimm SE, Pouwels X, Ramaekers BLT, Wijnen B, Knies S, Grutters J, et al. Development and Validation of the TRansparent Uncertainty ASsessmenT (TRUST) Tool for assessing uncertainties in health economic decision models. *Pharmacoeconomics* 2020;38(2):205-16.

[33] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. *Health Technol Assess* 2016;20(26):1-48.

[34] Health and Safety Executive. *Mesothelioma statistics for Great Britain 2020 [Internet]*. London: HSE, 2020 [accessed 2.2.21]. 12p. Available from: https://www.hse.gov.uk/statistics/causdis/mesothelioma/mesothelioma.pdf

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 26 March** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Abbreviation list

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Abbreviation list (page 3-5) The abbreviation list is inaccurate.	To update the abbreviation list to accurately reflect the contents of the assessment report.	The current abbreviation list has irrelevant abbreviations, including some that relate to breast cancer such as EGFR, PTC, NYHA, HER2+ and HR that are not relevant to this assessment report.	This is not a factual inaccuracy. Nevertheless, these abbreviations have been deleted.

Issue 2 Effectiveness and safety of expected nivolumab fixed dosing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 1.2 (page 12) The ERG requested evidence to support the relative efficacy and safety of the two dosing regimens. However, the evidence provided by the company lacked clarity or was not appropriate.	The ERG requested evidence to support the relative efficacy and safety of the two dosing regimens. The company provided results from a published poster of pharmacokinetic and clinical subgroup analyses of CM-743 by body weight which were used to support the flat-dose of nivolumab + ipilimumab.	It is factually inaccurate to state that the evidence provided by the company lacked clarity and was not appropriate and the company request that this wording is amended as suggested. In the company's clarification responses (dated 18 Feb 2021), a PDF copy of the Tsao et al. poster presented at ESMO 2020 was provided as an accompanying reference and is embedded here for your information.	Not a factual inaccuracy. As stated in the ERG report, AE rates at the given fixed dose were not provided, it is not clear to the ERG precisely how outcomes could be estimated for a fixed dose without evidence from patients who received that dosing regimen, and subgroup analyses by weight do not show the effect of patients receiving a lower or higher dose, as would have been the case if dosing had been weight-based.

		 Tsao_2020_ ESMO IO_743 flat dosing_2	

Issue 3 Immaturity of CheckMate-743 trial outcome

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 1.4 (page 13) The ERG asked for the results from a later data-cut, but the company stated that no further results were available and did not provide a date for their submission.	The company provided an estimated date range for the next OS datacut because it is an event-driven endpoint.	It is factually inaccurate to state that the company did not provide a date in the company clarification responses (dated 18 Feb 2021) and the company request that this wording is amended as suggested. In the company's clarification responses (dated 18 Feb 2021), the company provided a date range for the availability of the next data cut ([redacted]) – an exact date cannot be provided as the primary endpoint of OS is an event-driven endpoint.	Not a factual inaccuracy. The company stated: "However, follow up of CM-743 is ongoing and additional data cuts are expected, likely in [redacted] (TBC). This is not a date by which further results will be submitted to NICE.

Issue 4 Subsequent therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 1.5 (page 14) The ERG requested evidence as to the effect that the differences described above may have and	The ERG requested evidence as to the effect that the differences described above may have and for the comparison with English NHS practice.	It is factually inaccurate to claim that the ERG cannot validate the results versus UK clinical practice using the data provided in the company clarification	Not a factual inaccuracy. The ERG could not locate some of the figures reported by the company

for the comparison with English NHS practice. However, the ERG could not validate the results regarding time survived on subsequent therapy or the nature of that subsequent therapy.	The company provided real world data from the nationwide CAS study in England (Baas et al 2020), which was also validated by UK clinical experts. These data showed 784 patients received a 2nd line of therapy. Of these, 43.6% received SoC (platinum + pemetrexed), 18.6% received treatment in a clinical trial, and 24.1% received vinorelbine and showed that median OS was 8.5 months from start of second-line therapy and median treatment duration of second-line therapy was 1.6 months.	responses (dated 18 Feb 2021) and the company request that this wording is amended as suggested. The CAS registry data provides the best available real-world evidence with relevant data for the majority of patients with MPM in England, which was also validated by UK clinical experts. It is unclear why the additional data provided in the company's clarification responses are not sufficient to validate the results.	in the source cited, i.e. Baas et al 2020: [9] Baas P, Daumont MJ, Lacoin L, Penrod J, Carroll R, Tanna N. Treatment patterns and outcomes in malignant pleural mesothelioma in England: a nationwide CAS registry analysis from the I-O Optimise initiative. Poster presented at European Society for Medical Oncology (ESMO) Virtual Congress; 19-21 September 2020.
Section 3.2.4.6 (page 48): Subsequent systemic therapy was received by 44% and 41%;	Subsequent systemic therapy was received by 44% of patients in the nivolumab + ipilimumab arm and 41% in the PDC arm;	Incomplete part of sentence which could lead to misinterpretation of results.	Not a factual inaccuracy. The company have misunderstood the sentence, which is completed by "…patients in the nivolumab + ipilimumab arm and in the PDC arm respectively,…"
ERG comment (page 48): they cited real-world data from the CAS registry of patients with unresectable MPM in England from January 2013-December 2017, which showed that median OS was 8.5 months from start of second-line therapy and median treatment duration of second-line therapy was 1.6 months. However, the source provided and cited by the company does not seem to	The company cited real-world data from the CAS registry of patients with unresectable MPM in England from January 2013-December 2017, which showed that median OS was 8.5 months from start of second-line therapy and median treatment duration of second-line therapy was 1.6 months. The company also argued that the type of subsequent therapy employed in the trial was likely to be representative of English NHS practice, citing the same source as showing that of those who	It is factually inaccurate to state that the source provided do not report the data cited and the company request that this wording is amended as suggested. In the reference pack provided with the company submission, a PDF copy of the Baas et al. poster presented at ESMO 2020 was included, but it is also embedded here for your information.	Not a factual inaccuracy. The pdf included with the FAC is not the same as the only one provided in the reference pack with Baas 2020 in the name, i.e. Baas P 2020. Therefore, the ERG report has been amended accordingly .

report those numbers. The company also argued that the type of subsequent therapy employed in the trial was likely to be representative of English NHS practice, again citing the same source as showing that of those who received a second-line therapy, 43.6% received second-line PDC (platinum + pemetrexed), 18.6% received second-line treatment in a clinical trial, and 24.1% received second-line vinorelbine. However, these figures could not be located by the ERG in that source.	received a second-line therapy, 43.6% received second-line PDC (platinum + pemetrexed), 18.6% received second-line treatment in a clinical trial, and 24.1% received second-line vinorelbine.	 Baas et al CAS MPM_ESMO 2020 Pc	

Issue 5 Subgroup effectiveness of nivolumab + ipilimumab according to PD-L1 status and histology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 1.6 (page 14) Subgroup analysis by both PD-L1 status and histology, which was included in the scope, reveals potential variation and in some cases 95% CIs that overlap the point of no difference for nivolumab + ipilimumab versus PDC for both OS and PFS. This is particularly the case for PD-L1<1% where for PFS there is little uncertainty that PDC is	Subgroup analysis by both PD-L1 status and histology, which was included in the scope, reveals potential variation and in some cases 95% CIs that overlap the point of no difference for nivolumab + ipilimumab versus PDC for both OS and PFS.	Although the company acknowledges potential variation in the OS and PFS results in the PD-L1 and histology subgroups that will need to be discussed, it is factually inaccurate to state there is little uncertainty that PDC is superior for PFS for PD-L1<1% and that there is little difference between groups for OS. The company requests that this last sentence be removed as it	Not a factual inaccuracy. Nevertheless, the ERG have qualified this statement by reference to the 95% confidence intervals for the HR.

superior and for OS where there appears to be little difference between groups.		is factually inaccurate. Both in the company submission dossier and in the company's clarification responses (dated 18 Feb 2021) the considerable uncertainty of the clinical effectiveness results in the PD-L1<1% and histology subgroups was highlighted and that these results should be interpreted with caution.The uncertainty of these results was confirmed by two UK clinical experts. For PD-L1, uncertainty arises from problems with PD-L1 testing in MPM, uncertainty in PFS assessment in MPM and small patient numbers. Within the treatment group, a similar OS benefit was observed with nivolumab + ipilimumab regardless of PD-L1 expression (median OS of 17.3 months in PD-L1 < 1% and 18.0 months in PD-L1 ≥ 1%). PD-L1 was not a stratification factor in CheckMate-743; therefore, the data are limited by potential imbalances in known or unknown prognostic factors because the role of PD-L1 in MPM is unclear. Owing to the small sample size and event counts in the PD-L1– negative subgroup, the statistical analyses in the PD-L1 subgroups are descriptive in nature and should be interpreted with caution.	

Section 3.6 (page 50-52) In terms of OS, nivolumab + ipilimumab appears to be clearly more effective than PDC for MPM with PD-L1 ≥ 1% and for MPM with non-epithelioid histology. Although not so clear and with a reduced difference, nivolumab + ipilimumab also appears to be more effective than PDC for epithelioid histology. For PD-L1 <1% there appears to be little difference between the groups. In terms of PFS, nivolumab + ipilimumab appears to be clearly more effective than PDC for MPM with non-epithelioid histology. Although not so clear and with a reduced difference, nivolumab + ipilimumab also appears to be more effective than PDC for MPM with PD-L1 ≥ 1%. Nivolumab + ipilimumab appears to be clearly less effective than PDC for MPM with PD-L1 < 1%. Although not so clear and with a reduced difference, nivolumab + ipilimumab also appears to be less effective than PDC for MPM with epithelioid histology. ERG comment: In terms of OS, nivolumab + ipilimumab appears to be clearly more effective than	Section 3.6 (page 50- 51) In terms of the hazard ratio for OS, nivolumab + ipilimumab appears to be more effective than PDC for MPM with PD-L1 ≥ 1% and for MPM with non-epithelioid histology. Although with a reduced difference, nivolumab + ipilimumab also appears to be more effective than PDC for epithelioid histology. For PD-L1 <1% there appears to be little difference between the groups in terms of hazard ratio. In terms of the hazard ratio for PFS, nivolumab + ipilimumab appears to be more effective than PDC for MPM with non-epithelioid histology. Although with a reduced difference, nivolumab + ipilimumab also appears to be more effective than PDC for MPM with PD-L1 ≥ 1%. Nivolumab + ipilimumab appears to be less effective than PDC for MPM with PD-L1 < 1%. Although with a reduced difference, nivolumab + ipilimumab also appears to be less effective than PDC for MPM with epithelioid histology. ERG comment: In terms of the hazard ratio for OS, nivolumab + ipilimumab appears to be more effective than PDC in patients with MPM with PD-L1 ≥ 1% and in patients with MPM with non-epithelioid histology. Although with a reduced difference, nivolumab + ipilimumab also appears to be more effective than PDC, for epithelioid histology. There appears to be little	As above, the company acknowledges the potential variation in the OS and PFS results in the PD-L1 and histology subgroups that will need to be discussed, it is factually inaccurate to state that it is **clearly** more effective. The company requests that this wording be removed as it is factually inaccurate for the reasons stated above. Due to the limitations in PFS assessment, PDL-1 testing and histological subtyping in MPM discussed in detail in the company submission and highlighted by UK clinical experts, there is considerable uncertainty in the results of the histological and PD-L1 subgroups in CheckMate-743, which should be interpreted with caution.	

PDC in patients with MPM with PD-L1 ≥ 1% and in patients with MPM with non-epithelioid histology. Although not so clear and with a reduced difference, nivolumab + ipilimumab also appears to be more effective than PDC, for epithelioid histology. There appears to be little difference between treatments for PD-L1 < 1%. In terms of PFS, nivolumab + ipilimumab appears to be clearly more effective than PDC for MPM with non-epithelioid histology. Although not so clear and with a reduced difference, nivolumab + ipilimumab also appears to be more effective than PDC for MPM with PD-L1 ≥ 1%. Nivolumab + ipilimumab appears to be clearly less effective than PDC for MPM with PD-L1 < 1%. Although not so clear and with a reduced difference, nivolumab + ipilimumab also appears to be less effective than PDC for MPM with epithelioid histology.	difference between treatments for PD-L1 < 1%. In terms of the hazard ratio PFS, nivolumab + ipilimumab appears to be more effective than PDC for MPM with non-epithelioid histology. Although with a reduced difference, nivolumab + ipilimumab also appears to be more effective than PDC for MPM with PD-L1 ≥ 1%. Nivolumab + ipilimumab appears to be less effective than PDC for MPM with PD-L1 < 1%. Although not so clear and with a reduced difference, nivolumab + ipilimumab also appears to be less effective than PDC for MPM with epithelioid histology.		

Issue 6 Treatment effectiveness and extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 1.10 (page 16) Alternative approaches to estimate PFS and OS as well as assumptions related to treatment waning are considered by the ERG. Section 4.2.6.1 (page 60) Seven parametric models were considered for the extrapolation of PFS and OS (exponential, Weibull, Gompertz, log normal, log-logistic, gamma, and generalised gamma). Section 4.2.6.4 (page 62) The selection of a piecewise approach to estimate OS for both nivolumab + ipilimumab and PDC was clarified in response to clarification question B5. Section 4.2.6.4 (page 63) Given the abovementioned limitations of the company's piecewise approach and the lack of justifications for the selecting the distributions for the piecewise approach, the ERG prefers to use a standard parametric approach to estimate OS in its base-case. Specifically, the log-	Table 1.10 (page 16) Alternative approaches to estimate PFS and OS as well as assumptions related to treatment waning were provided by the company and considered by the ERG, including spline models as an alternative approach to the piecewise models to estimate OS extrapolation. Section 4.2.6.1 (page 60) Seven parametric models were considered for the extrapolation of PFS and OS (exponential, Weibull, Gompertz, log normal, log-logistic, gamma, and generalised gamma). In addition, six spline-based models were considered for OS (1 and 2 knot models using the hazard, odds, and normal scales). Section 4.2.6.4 (page 62) The selection of a piecewise approach to estimate OS for both nivolumab + ipilimumab and PDC was clarified in response to clarification question B5 and the company provided an alternative approach using spline models. Section 4.2.6.4 (page 63) Given the abovementioned limitations of the company's piecewise approach,	It is factually inaccurate to state that only the piecewise and standard parametric approaches were considered, when the company (at the request of the ERG) also considered spline models in their clarification responses (dated 18 Feb 2021). The company request that the full exploration of spline modelling provided by the company in response to the ERG clarification question B5 are fully critiqued by the ERG and these considerations are included in the assessment report for completeness. Currently these are not included in the assessment report and we believe that their omission will hinder a full discussion of this issue at technical engagement stage and current wording does not reflect all the additional extrapolation options that were provided by the company in their clarification responses.	Not a factual inaccuracy. The summary sections of the ERG report summarise the CS and not the clarification responses, which are typically considered in the ERG critique if appropriate. However as always, the ERG has to balance being concise and complete and therefore focusses on the most important aspects. What is considered most important might be a matter of judgement. As mentioned in the ERG report, the fit to the observed data/"within-trial fit" (for the estimated PFS and OS) is probably not as important as the long-term extrapolation. The plausibility of the long-term extrapolation of the spline-models was not considered in detail nor were the spline-models adopted in a (revised) CS base-case (thus these should be considered as scenario analyses). For these reasons, the ERG opted not to discuss spline-models in the ERG report.

logistic distribution for both treatment arms is considered a plausible alternative, as illustrated in CS.	alternative spline modelling approaches were provided by the company.		

Issue 7 Company's cost effectiveness results – proportion of (PF)LY accumulated beyond the observed data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 1.10 (page 18) Providing additional explanation of the mechanism by which the model generated the differences as well as a justification for why they are plausible based upon available evidence is warranted. This includes verifying the plausibility of the partitioned survival model extrapolations.	The company provided justification for the inclusion of all external data in model, including the plausibility of the chosen model extrapolations, which was validated with UK clinical experts provided in Appendix N; further justification was provided in clarification responses.	It is factually inaccurate to claim that additional explanation and justification is warranted, as this was provided in the company clarification responses (dated 18 Feb 2021) and the company request that this wording is amended as suggested. Justification for all external data included in the model was provided in the company submission, which was also validated by UK clinical experts. It is unclear why the additional information provided in the company's clarification responses (dated 18 Feb 2021) are not sufficient to validate the results.	Not a factual inaccuracy. Presumably the company is referring to Table 1.15 (not Table 1.10). As mentioned in Table 1.15 the large majority of (PF)LY is accumulated beyond the observed data and this is substantially larger for nivolumab + ipilimumab than for PDC. While the company's responses to clarification questions B5 and B8 give some indication about the plausibility of the long-term extrapolations, the findings presented in Table 5.2 of the ERG report indicate that the large majority of gains are accumulated beyond the observed data period and hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available

			evidence is warranted (see recommendation 13 in NICE DSU technical support document 19 on partitioned survival analysis). This includes verifying the plausibility of the partitioned survival model extrapolations (see ERG report Section 4.2.2). This was requested but not provided in the company's response to clarification question B17.

Issue 8 Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 24. Regulatory approval and marketing authorisation are expected in [redacted]	Regulatory approval and marketing authorisation are expected on or around [redacted]	Updated date for marketing authorisation.	Not a factual inaccuracy. The change in wording is not indicate a substantive difference to the information already provided in the ERG report.

Issue 9 CheckMate-743 Baseline Characteristics

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG comment (page 36): However, the CheckMate-743 had just 38 patients from the UK , which was 6.3% of total patients randomised.	However, the CheckMate-743 had 38 patients from 6 sites in the UK, which was 6.3% of total patients randomized.	Addition of further relevant information.	Not a factual inaccuracy. The ERG does not consider that the additional information will have any substantive effect on any

			conclusions regarding applicability to UK clinical practice.

Issue 10 Company's subgroup analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59. ERG comment (b): In response to clarification question B3, the company explained that it did *"not consider economic modelling of nivolumab + ipilimumab by histological subtype or PD-L1 expression as appropriate, given the high clinical unmet need of all patients with unresectable MPM eligible for SACT and the OS benefit seen in all subgroups in CheckMate-743."*	In response to clarification question B3, the company explained that *"a high proportion of patients with MPM in real-life clinical practice in the UK have unknown or not otherwise specified (NOS) histology, while PD-L1 testing is not standardised and not an established predictive biomarker in MPM. As such the company does not consider economic modelling of nivolumab + ipilimumab by histological subtype or PD-L1 expression as appropriate, given the high clinical unmet need of all patients with unresectable MPM eligible for SACT and the OS benefit seen in all subgroups in CheckMate-743."*	The company requests that all the arguments presented in the clarification document are included in the ERG assessment report as a fair representation of the company reasons for not performing cost-effectiveness analyses for the PD-L1 and histological subtypes.	Not a factual inaccuracy. This was a direct quote from the clarification response.
Section 5.1.1 (C) (page 73): tests for interactions were unfortunately not provided by the company, despite requested in clarification question A13.	tests for interactions were unfortunately not performed by the company, despite requested in clarification question A13. The reasons given by the company were that patient and event numbers in the PD-L1 and non-epithelioid subgroups were small, not prespecified	The company requests that all the arguments presented in the clarification document are included in the ERG assessment report as a fair representation of the company reasons for not performing these analyses.	Not a factual inaccuracy.

	and not powered; therefore, any statistical analyses in the subgroups are descriptive requested was not reported for CheckMate-743.		

Issue 11 Adverse event costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.9.5 (d) (page 70) The company did not provide cost effectiveness analyses with all-causality (treatment-emergent) AEs instead of only treatment-related AEs, and the restriction on the incidence changed to 1% as requested by the ERG in the clarification letter.	The company did not provide cost effectiveness analyses with all-causality (treatment-emergent) AEs instead of only treatment-related AEs, and the restriction on the incidence changed to 1% as requested by the ERG in the clarification letter. The reason given by the company was on the basis of the very low incidence of these events and the small differences between treatment arms, meaning the impact to the ICER would be minor; in addition, relevant cost and disutility data were not available for many of these adverse events.	The company requests that all the arguments presented in the clarification document are included in the ERG assessment report as a fair representation of the company reasons for not performing these analyses.	Not a factual inaccuracy.

Issue 12 Comparison with other technology appraisals

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.3 (page 76) No comparisons with other technology appraisals were provided	No comparisons with other technology appraisals were provided. The reason given by the company was that there were no other relevant appraisals for MPM as there has not been any other immunotherapy assessed by NICE in this indication.	The company requests that all the arguments presented in the clarification document are included in the ERG assessment report as a fair representation of the company reasons for not performing these comparisons.	Not a factual inaccuracy.

Issue 13 ERG base-case – Matter of judgement 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 6.2 (page 82) The ICER for "Matter of judgement 2: use log-logistic distributions for OS in both treatment arms (not piecewise) (key issue 9)" is incorrect.	Using the log-logistic distributions for OS in both treatment arms (not piecewise) results in an ICER of £91,596, not £92,413. The results for this analysis should be updated.	Error in reported results.	The ICER is correct but unfortunately the description is indeed incorrect and "not piecewise" should read "using piecewise". This error also affected Table 1.16 and has been corrected in both instances.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Table 1.6 (page 14) [redacted]	These data are not marked as AIC in the latest version of the company submission dossier dated 18 Feb 2021.	This is particularly the case for PD-L1<1% where for PFS there is little uncertainty that PDC is superior and for OS where there appears to be little difference between groups. However, as stated above in factual inaccuracies, we consider that this statement is inaccurate and should be removed.	Amended.
[redacted] in Table 3.5, Table 3.7, page 39, Table 3.9, Table 3.10, Table 3.12, page 48, Table 3.13, page 49, Table 3.14, page 50, page 51, page 52	These data are not marked as AIC in the latest version of the company submission dossier dated 18 Feb 2021.	No AIC marking of CheckMate-743 results is needed.	Amended.
Section 2.3 page 26: In the UK in 2019, only two patients (1%) received combination treatment with off-label raltitrexed.	These data are as yet unpublished and should be marked as AIC, as marked up in the clarification responses,	In the UK in 2019, [redacted] received combination treatment with off-label raltitrexed.	Amended.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **Wednesday 19 May 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
  - Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Eleni Theodorou**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bristol Myers Squibb Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key Issue	Does This Response Contain New Evidence, Data Or Analyses?	Response
Additional questions received on 12 May		The company has initiated work to assess the impact of switching from PDC to immunotherapy in the trial, after it was highlighted in an email received from NICE on 12th May 2021 that the impact on both OS and the ICER should be explored. Due to the limited time available, it has not been possible to conduct a full assessment for inclusion in this response. However, an initial assessment indicates that adjusting for immunotherapy following PDC will improve the treatment effect for nivolumab + ipilimumab and therefore reduce the ICERs. Regarding the differences between the rates of subsequent treatments reported in the CSR (table 6.5.3-1) and those that the company noted were used in the economic model (table 44 of the CS), the 9 most common subsequent treatments were included in the model. However, the total sum of all subsequent treatments was greater than 100%. A decision was made to reweight the proportion receiving each of the 9 included subsequent treatments to sum to 100%. Additionally, the CSR reports the proportion of the total arm (e.g. 41 out of 302 = 13.6%), however, the model used the proportion of those receiving subsequent systemic therapy, which was 123, making 123 the denominator.

Key issue 1: Effectiveness and safety of expected nivolumab fixed dosing	**YES**	As noted in the company submission and response to clarification questions, the dosing and schedule of nivolumab in CheckMate-743 (3 mg/kg every 2 weeks) differs from the proposed indicated dose and schedule of nivolumab submitted to the European Medicines Agency (EMA) and included in the CHMP positive opinion (22 April, 2021; 360 mg every 3 weeks). Based on the totality of pharmacokinetic modelling of nivolumab exposure, exposure-efficacy, exposure-safety, and clinical subgroup efficacy and safety analyses, the balance of benefits and risks of nivolumab 360 mg Q3W is expected to be similar to that of nivolumab 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W for the treatment of untreated unresectable MPM. 'academic/commercial in confidence information removed' The EMA has accepted a change from weight-based to flat dosing in a number of other nivolumab indications, including second-line NSCLC and cancer of the head and neck and this was not considered an issue when discussed during appraisal (TA490). After their rigorous assessment of the available data, the EMA accept that the flat dosing of nivolumab provides equivalent efficacy and safety to the weight-based dosing in trials, the SmPC states: "Based on modelling of dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between a nivolumab dose of 240 mg every 2 weeks or 3 mg/kg every 2 weeks. Additionally, based on these relationships, there were no clinically significant differences between a nivolumab dose of 480 mg every 4 weeks or 3 mg/kg every 2 weeks in adjuvant treatment of melanoma, advanced melanoma and advanced RCC" (EMA, 2021). Because the EMA's role is to ensure the efficacy and safety of medicines available in Europe, their recommendation should also inform NICE's assessment.
Key issue 2: Applicability of comparator to English NHS practice	**NO**	The most relevant data on current treatment practice in the NHS in England come from the national Cancer Analysis System (CAS) registry that includes **all** patients newly diagnosed with MPM in England between January 2013 and December 2017 (Baas et al., 2020). Because no new treatments have been approved in MPM since December 2020, this analysis represents the best possible evidence for the current treatment pathway in England. Of the 2,810 patients who received first-line therapy with a platinum + pemetrexed, 'academic/commercial in confidence information removed'

		These data for all MPM patients treated with first-line chemotherapy in England are similar to those reported in the CheckMate-743 trial (Baas et al., 2021). After randomisation, 104 (34%) of 302 patients in the chemotherapy group were given cisplatin and 180 (60%) were given carboplatin; 29 (28%) of 104 patients given cisplatin switched to carboplatin after the first dose due to investigator decision. Therefore, overall, 74% of patients were treated with carboplatin and 37% with cisplatin.
Key issue 3: Immaturity of CheckMate-743 trial outcomes	**NO**	New data cuts of CheckMate-743 are planned in 'academic/commercial in confidence information removed', if new analyses are available before the appraisal committee meeting, we will provide them as additional evidence.
Key issue 4: Subsequent therapy: difference between arms and applicability to English NHS practice	**NO**	As provided in response to clarification questions, in CheckMate-743, after study treatment was discontinued, similar proportions of patients in each treatment arm received subsequent therapy: 44.2% of those treated with nivolumab + ipilimumab subjects and 40.7% of those treated with PDC (Baas et al., 2021). Most subjects received subsequent chemotherapy (43.2% and 31.5% from the nivolumab + ipilimumab and PDC arms, respectively). Subsequent immunotherapy (anti–PD-1/PD-L1, anti-CTLA-4, other) was received by 3.3% of the nivolumab + ipilimumab and 20.2% of the PDC arm, respectively. A small percentage of subjects received subsequent experimental therapies (0.7% and 4.0% in the nivolumab + ipilimumab and PDC arms, respectively). During technical engagement, a clinician was asked what percentage of patients receive subsequent therapy in England, he estimated 30% of PDC-treated patients and 35% of nivolumab + ipilimumab-treated patients would receive second line therapy. In CheckMate-743, more patients received subsequent immunotherapy after PDC than with nivolumab + ipilimumab, which is expected since use of a subsequent therapy with a different mode of action to prior treatment is standard clinical practice. Patients with MPM treated with second-line therapies have a short life expectancy, and therefore duration of subsequent treatments is also short. Real-world data from the CAS registry of patients with unresectable MPM in England from January 2013-December 2017 showed that median OS was 8.5 months from start of second-line therapy and median treatment duration of second-line therapy was 1.6 months (Baas et al., 2020). For the

		company submission, this assumption was validated by UK clinical experts. There are currently no second-line therapies licensed for use in MPM as no second-line therapy has shown a survival benefit in MPM in a randomised controlled trial with an active comparator. However, nivolumab monotherapy is being used in the NHSE in England under interim treatment options during the COVID-19 pandemic (NICE, 2021). Based on this interim guidance, from August 2020 to April 2021, 388 patients were treated with nivolumab monotherapy in this indication. Preliminary results of the phase 3 CONFIRM trial of nivolumab versus placebo in relapsed MPM confirm the registry data in terms of the duration of subsequent therapy (Fennell et al., 2021). The median duration of treatment was 84 days in the nivolumab arm (n = 221) and 43 days in the placebo arm (n = 111). During technical engagement, the durations of therapy were again validated with a UK clinician who noted that there are no subsequent therapies approved in the UK (other than nivolumab monotherapy due to COVID-19), but anticipated that those who received subsequent therapy would have it for between 1 and 3 months (approximately 1-2 months for gemcitabine, 2 months for vinorelbine, 2.5 months for PDC, and 2-3 months for nivolumab monotherapy). Overall, the company considers that any confounding of OS due to subsequent treatments is likely to be biased in favour of the PDC arm, resulting in an underestimate of the incremental improvement in OS reported for nivolumab + ipilimumab. As noted earlier the company has initiated work to assess the impact of switching from PDC to immunotherapy in the trial. The initial assessment indicates that adjusting for immunotherapy following PDC will improve the treatment effect for nivolumab + ipilimumab.
Key issue 5: Subgroup effectiveness of nivolumab + ipilimumab according to PD-L1 status and histology	**NO**	Patients with MPM have a poor prognosis with current treatments, with low 3-year survival rates of approximately 10% across all disease stages and histological subtypes. There is therefore a high unmet clinical need for all patients with MPM, regardless of histological subtype or level of PD-L1 expression. As stated in our response to clarification questions, evidence for the levels of PD-L1 expression in patients with MPM in England is inconsistent, with wide variation in the threshold cut-offs used and the rates of PD-L1 expression observed in clinical studies (see Table 3 in

		Document B, p17). As a result, large differences have been reported, with 20% to 70% of specimens tested being considered PD-L1–positive. Unlike other lung cancers in which PD-L1 inhibitors are already approved and PD-L1 testing is standard practice, PD-L1 testing is not routinely performed on biopsies from patients with MPM in the NHS in England, and the thresholds, scoring methods, and antibodies used to detect PD-L1 expression in MPM are not standardised which may contribute to this variation. Reliable PD-L1 testing is highly dependent on biopsy, which is technically difficult in MPM because MPM tumours have spatial heterogeneity and the amount of tissue obtained is usually not sufficient for accurate PD-L1 testing. For these reasons and because until now no PD-L1 inhibitor has shown benefit in MPM in the first-line setting, PD-L1 testing is not currently a standard test in the NHS for this patient population (see clinical expert opinion: Appendix N of the company submission). PD-L1 was not a stratification factor in CheckMate-743; therefore, the data for PD-L1 subgroups are limited by potential imbalances in known or unknown prognostic factors and because the role of PD-L1 in MPM is unclear. Although the OS benefit with nivolumab + ipilimumab versus PDC was greater in patients with PD-L1 ≥ 1% (HR, 0.69; 95% CI, 0.55-0.87) than in patients with PD-L1 < 1% (HR, 0.94; 95% CI, 0.62-1.40). within the treatment group, similar OS was observed with nivolumab + ipilimumab regardless of PD-L1 expression (median OS of 17.3 months in PD-L1 < 1% and 18.0 months in PD-L1 ≥ 1%). Owing to the small sample size and event counts in the PD-L1–negative subgroup, the statistical analyses in the PD-L1 subgroups are descriptive in nature and should be interpreted with caution. In addition, due to the severe limitations in PD-L1 testing in MPM and the survival seen in both PD-L1 < 1% and ≥ 1% subgroups in CheckMate-743, the company does not consider patient selection criteria for nivolumab + ipilimumab by levels of PD-L1 expression as appropriate, given the high clinical unmet need and short life expectancy of all patients with unresectable MPM eligible for SACT. Histological subtype (epithelioid or non-epithelioid) was a stratification factor in CheckMate-743, as presented in the Company Submission, an OS benefit was observed in epithelioid and non-epithelioid subgroups, with similar median OS for nivolumab + ipilimumab in both histology subgroups. The treatment effect of nivolumab + ipilimumab versus PDC was more pronounced in the non-epithelioid subgroup (HR, 0.46) than in the epithelioid subgroup (HR,

		0.86), driven by the known poorer performance of PDC in the non-epithelioid subgroup. Nonetheless, there remain issues with histological typing in MPM, meaning subgroups should not be used in decision making in this indication. In clinical practice in the UK, a high proportion of patients with MPM have unknown or not otherwise specified (NOS) histology. Real-world data from the CAS registry in England from January 2013-December 2017 (Baas et al., 2020) showed that of 2,810 patients who received first-line pemetrexed + platinum-based therapy, 34.5% had histology that was not otherwise specified and 3.2% were unknown subtype. Reasons given for this by UK clinical experts were the technical difficulties with obtaining a biopsy in MPM and that histological subtype can be a broad spectrum that is hard to define (Company submission, Appendix N). For these reasons, the company considers the outcomes in the histological subgroups in CheckMate-743 as descriptive in nature and should be interpreted with caution. In addition, the company does not consider patient selection criteria for nivolumab + ipilimumab by histological subtype as appropriate, given the limitations in histological subtyping in real-life clinical practice; the significant OS benefit seen in both epithelioid and non-epithelioid subgroups in CheckMate-743 and the high clinical unmet need of all patients with unresectable MPM eligible for SACT. Because there are inherent issues in terms of subgroup analyses by both PD-L1 and histology, analyses that combine these two subgroups would be inappropriate, result in increased uncertainty and have not therefore been undertaken. Additional data cuts of CheckMate-743 are not yet available; BMS will be able to provide analyses from these as they become available. The use of subgroups in decision making was discussed with a clinical expert during technical engagement. The clinician considered that there is an unmet need for new treatments for all patients with MPM and determining access to nivolumab + ipilimumab based on subgroups would exclude patients who would benefit from it – the level of OS benefit in the entire intention-to-treat population has never been seen in other studies in MPM. Furthermore, because CheckMate-743 was not powered for these subgroup analyses, differences in the efficacy results in subgroups may have been caused by chance. Therefore, while subgroup

		analyses are interesting, they are intended to drive further research and are not appropriate for use in clinical decision making.
Key issue 6: Model structure - the use of a partitioned survival model (PSM), without a state transition model (STM) approach to verify the results	**NO**	As presented in the response to the ERG's clarification questions multiple model structures were considered during the development of the economic model, including state transition modelling. As presented in our previous response, a virtual European advisory board for the economic modelling of nivolumab + ipilimumab in 1L MPM was carried out in November 2020 and consisted of 12 experts across Europe, including 4 from the UK (one clinical oncologist, one clinical senior lecturer, one professor of medical statistics and one senior research fellow). Advisors agreed that partitioned survival models (PSM) were widely accepted by HTA bodies due to their straightforward approach and their use of data taken directly from the trials (OS and PFS); and most advisors agreed with a PSM being used for nivolumab + ipilimumab in 1L MPM. Therefore, based on data availability, input from health economic advisory boards and to be aligned with previous NICE cancer appraisals, a partitioned survival model was chosen. We would also like to point out that in the specific recommendation the ERG refers to for presenting a state transition model the DSU also concludes that state transition models cannot be recommended over partitioned survival models, given the need for further research around state transition models. Further, it is also pointed out that, although state transition models might have some benefits over partitioned survival models (given they model health state occupancy more explicitly), long-term predictions are still dependent on the within-trial trends in individual transition rates being representative of post-trial trends. We are not aware of, and the ERG has not presented, evidence that shows that extrapolations from state transition models in general would provide more precise long-term extrapolations compared with partitioned survival models and thus address the ERGs comment about majority of results being generated beyond the trial follow up. On the contrary, the DSU highlight that methodological development is needed around how the model fit for state transition models should be assessed. This given that typical model outputs to which a good fit is expected (e.g., OS) is based on a composite of multiple fitted survival functions in a state transition model. Presenting a state transition model in addition to the submitted model would have required an

		unreasonable amount of work, including the need for clinical validation of all analyses resulting from such a model in addition to the partitioned survival model already presented.
Key issue 7: Population – no subgroup cost effectiveness analyses presented	**NO**	As described in detail in response to Issue 5, there is an unmet need for effective treatments in all patients with MPM, and in CheckMate-743, efficacy benefits were seen in the entire intention-to-treat population. There are issues in terms of the assessment of both PD-L1 and histology in patients with MPM that mean they are unreliable, and analyses of combined subgroups would add further uncertainty. Therefore, decision making should be based on the entire population eligible for nivolumab + ipilimumab in this indication.
Key issue 8: Intervention & comparators – two-year stopping rule may not be completely adhered to in trial	**NO**	In practice in the UK, the 24-month stopping rule is routinely used in multiple indications across IOs and information from NHSE in previous appraisals suggests that this is adhered to. We agree with the ERG that the 2 patients in CheckMate-743 who remained on therapy after 24 months will have minimal impact on model results, and based on NHSE input to previous appraisals, will not be an issue in clinical practice.
Key issue 9: Treatment effectiveness and extrapolation – immaturity of the long-term progression-free survival (PFS) and overall survival (OS) data	**YES**	**<u>Extrapolation of PDC OS</u>** With regards to the choice of parametric distribution for modelling of the PDC arm, as with the nivolumab + ipilimumab arm, a key selection criterion was the clinical plausibility of the long-term survival. We agree with the ERG that the log-logistic distribution provides clinically plausible survival predictions for nivolumab and ipilimumab. However, as presented in the company submission we do not agree that selection of the log-logistic distribution for PDC results in clinically plausible survival predictions. We agree that the hybrid approach originally selected has some areas of uncertainty as presented by the ERG and thus explored spline models per the ERG's request as part of the clarification questions. As presented in our response to the clarification questions, some of the spline models provided improved fit to the trial data compared with the standard parametric functions as well as clinically plausible long-term predictions. Given the improved within-trial fit of these models compared with the exponential model, while also providing clinically plausible long-term predictions they could be considered preferable to the exponential. Use of spline models would thereby negate the need for a piecewise model to be applied to improve fit for the within-trial period. Thus, scenarios without piecewise modelling for both arms were presented in our response to the clarification

questions with spline 2 knots hazard, spline 1-knot normal, and 2-knots normal used for PDC.

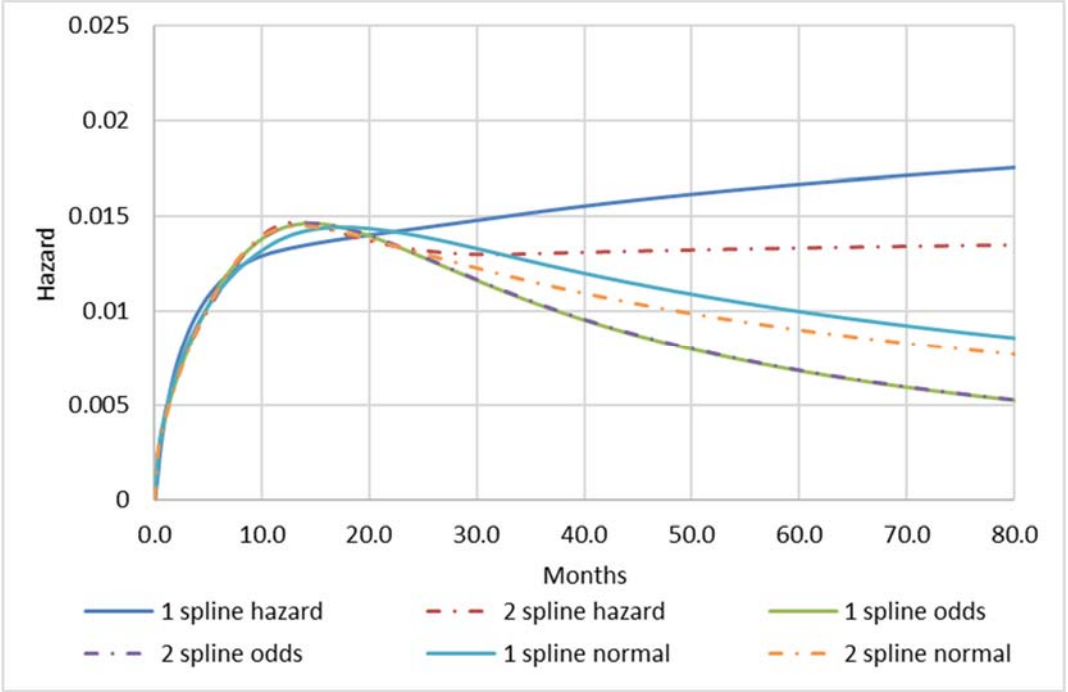
Since submission of our response to the clarification questions, further assessment and validation of the spline models has been conducted with input from a UK clinical expert. Based on this further validation an updated version of Table 1 in the company submission for PDC survival extrapolations is presented below.

Table 1. Summary of Assessment of Selection Criteria for Distributions for PDC Overall Survival

Distribution	AIC	BIC	Over/under-estimates of median survival	Appropriate hazard function	Plausible survival predictions
Weibull	✓	✓	↑	✗	✗
Gamma	✓	✓	↑	✗	✗
Gompertz	✗	✗	↑	✗	✗
Generalised gamma	✓	✓	↑	-[a]	-
Exponential	✗	✗	↓	✗	✓
Log-logistic	✓	✓	↓	✓	✗
Log-normal	✗	✗	↓	✓	✗
Spline 1-knot hazard	✓	✓	↑	✗	✗
Spline 2 knots hazard	✓	✓	↑	✗	✓
Spline 1-knot odds	✓	✓	↑	✓	✗

		Spline 2 knots odds	✓	✓	↑	✓	✗
		Spline 1-knot normal	✓	✓	↑	✓	✓
		Spline 2 knots normal	✓	✓	↑	✓	✓
		As can be seen from the table, all spline models provide a reasonable fit to the within-trial data. However, as presented in the table and in Figure 1 the spline hazard models did not have a hazard function with an initial increase and decreases over time in line with the MAPS data.					

Figure 1. PDC Independent Spline Hazard Function



As presented in the response to clarification questions and the company submission the clinical experts consulted during the development of the company submission considered that rates of 5-year, 7.5-year and 10-year survival for PDC patients would be 5%, 2% and 0%, respectively. With regards to predicted survival, spline 1-knot hazard and spline 1 and 2 knots odds were therefore considered not to be appropriate (resulting in 3%, 6% and 6% survival at 5 years, respectively, and with patients surviving until 15 years with spline 1 and 2 knots odds). However, spline 2 knots hazard and spline 1 and 2 knots normal resulted in clinically plausible long-term survival. Of these, spline 2 knots normal might be seen to be on the high end, and 2-knots hazards on the lower end for 5- and 10-year survival.

To inform the selection of the most clinically plausible survival extrapolation, the spline models fitted were validated with a UK clinical expert. Landmark survival estimates from these models were presented together with predicted survival from the log-logistic distribution preferred by the ERG. The clinical expert stated that the survival predictions from the log-logistic distribution would be too optimistic and that survival would be < 2% at Year 10. This is also aligned with prior clinical input received where 10-year survival for PDC was thought to be 0%. Of the distributions fitted to the PDC data, the clinical expert selected the spline 2-knots normal as the most appropriate but stated that some of the other spline models predicting similar low long-term survival are also plausible.

Based on the overall assessment presented in Table 2 as well as the clinical validation, Spline 2-knots normal has therefore been selected as the new base case extrapolation for the PDC arm. It is also clear from the clinical validation that the log-logistic distribution selected for PDC by the ERG results in clinically implausible long-term survival predictions.

Table 2. Absolute OS Analysis for Independent Models Fitted to Pemetrexed + Cisplatin or Carboplatin

		Absolute Survival (%)								
Data Set	Curve	6 mos	Year 1	Year 2	Year 3	Year 5	Year 10	Year 15	Year 20	Median (mos)
CheckMate 743	Kaplan-Meier	82.2	57.7	27.0	15.2	-	-	-	-	14.10
Zalcman 2016 (MAPS) pemetrexed + cisplatin	Kaplan-Meier	88.8	63.4	33.6	15.7	8.1	-	-	-	16.1
	Log-logistic	81.7	57.3	28.6	16.5	7.5	2.4	1.2	0.7	13.80

Pemetrexed + cisplatin/ carboplatin extrapolation	Spline 1-knot hazard	81.1	58.5	28.1	13.0	2.5	0.0	0.0	0.0	14.72
	Spline 2-knots hazard	82.1	58.2	27.7	14.1	3.6	0.1	0.0	0.0	14.49
	Spline 1-knot odds	82.0	58.1	27.5	15.1	6.3	1.8	0.8	0.5	14.49
	Spline 2-knots odds	82.1	58.1	27.5	15.0	6.3	1.8	0.8	0.5	14.49
	Spline 1-knot normal	81.8	58.7	27.6	13.9	4.4	0.5	0.1	0.0	14.72
	Spline 2-knots normal	82.1	58.0	27.6	14.6	5.1	0.8	0.2	0.0	14.49

Modelling of long-term treatment effect

As presented in the company submission and reiterated in the company response to clarification questions, there is long-term evidence of a robust and durable treatment effect lasting beyond discontinuation for immunotherapies. This robust and durable treatment effect lasting beyond discontinuation for immunotherapies has been shown in several indications for immunotherapies (NICE TA357, NICE TA366, NICE TA384, NICE TA400, NICE TA553, NICE TA558). Further, it is important to bear in mind that any modelling of changes of treatment effect with time directly effects the long-term survival extrapolations.

As presented in the company submission, the company response to clarification questions and in this document, selection of the most appropriate survival curves to be used in the model has

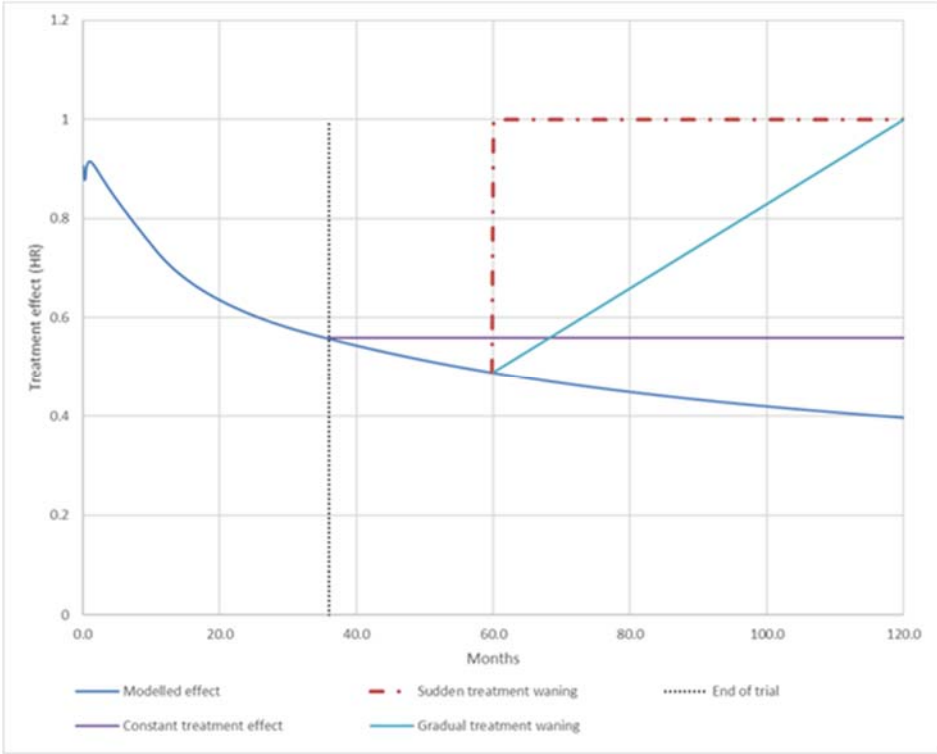
been guided by clinical input on the plausibility of long-term survival. Based on this input the log-logistic distribution was perceived as providing the most clinically plausible long-term predictions for nivolumab + ipilimumab and Spline 2-knots normal for PDC. As can be seen from Table 3, the incorporation of treatment waning as proposed by the ERG would result in a significant reduction in the proportion of patients estimated to be alive at 10 years. Therefore, predicted OS for nivolumab + ipilimumab would no longer be clinically plausible as advised by the clinical experts in preparation of the company submission. This highlights that the treatment effect and extrapolations cannot be considered in isolation; the overall clinical plausibility of the extrapolations needs to be the primary basis for validation, considering both the distributions for extrapolation and any waning of treatment effect.

Table 3. Absolute OS Estimates for Nivolumab + Ipilimumab With Different Treatment Effect Waning Scenarios

	Absolute Survival (%)					
Scenario	**6 mos**	**Year 1**	**Year 2**	**Year 3**	**Year 5**	**Year 10**
Modelled without treatment waning	84.0%	65.2%	40.1%	26.8%	14.6%	5.7%
ERG proposed sudden treatment waning from Year 5	84.0%	65.2%	40.1%	26.8%	14.6%	2.2%
Constant treatment effect from Year 5	84.0%	65.2%	40.1%	26.8%	14.6%	5.2%

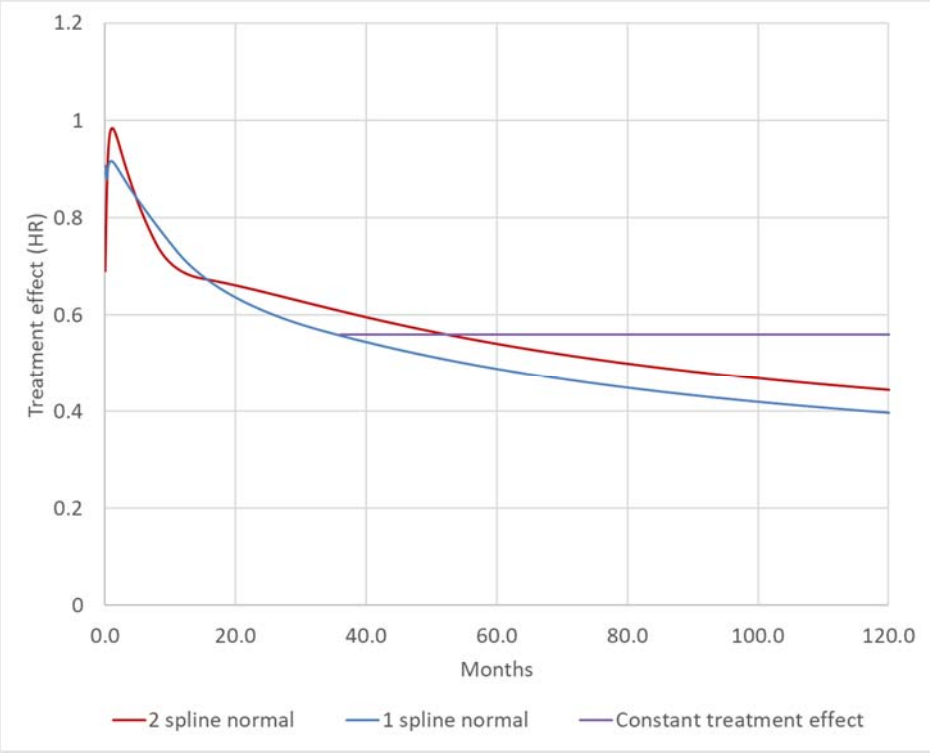
		To further inform the modelling of long-term treatment effect clinical expert advice was sought in preparation of this response. The clinical expert was presented with alternative scenarios of treatment effect over time (Figure 2) to assess what is most clinically plausible. The clinical expert reiterated what was presented in the company submission that he would anticipate a durable treatment effect with a dual immunotherapy treatment, as has been observed in other indications, with a proportion of patients having a long-term durable response. Whereas all benefits from PDC were predicted to be lost by Year 5. Of the presented assumptions of treatment effect over time the clinical expert thought that the ERG proposed sudden loss of treatment effect was unthinkable and lacked clinical validity. He thought that the presented modelled treatment effect (based on log-logistic for nivolumab + ipilimumab and spline 1-knot normal for PDC) seemed a bit optimistic and that the continued constant treatment effect would be the worst-case scenario. Thus, he stated that the most likely treatment effect over time would be somewhere in between the two scenarios. Based on this clinical input we argue that the suggested waning by the ERG lacks clinical plausibility. Further, as noted earlier we argue that waning of treatment effect cannot be viewed in isolation from the selected survival extrapolation. Figure 3 presents the resulting treatment effect from the economic model with the distributions deemed to be the most clinically plausible (updated company base case) together with the scenario presented to the clinical expert. As can be seen from the figure the updated base case (log-logistic for nivolumab + ipilimumab and spline 2-knot normal for PDC) in fact result in a long-term treatment effect in more in line with what the clinical expert thought would be the most clinically plausible long-term treatment effect.

Figure 2. Plot of Hazard Ratio Over Time Under Different Waning of Treatment Effect Assumptions



Note: Modelled effect is based on log-logistic for nivolumab + ipilimumab and spline 1-knot normal for PDC.

Figure 3. Plot of Hazard Ratio Over Time With 1 and 2-Knots Spline Normal Selected for PDC Extrapolation



Therefore, based on the clinical input provided, the log-logistic distribution without waning results in the most appropriate distribution to use for nivolumab + ipilimumab (to which the ERG agreed) and thus should be seen to adequately capture the long-term survival without treatment waning being applied. However, as a conservative scenario analysis the assumption of constant treatment effect from Year 5 has been investigated resulting in increased revised base case ICER from £77,669 to £81,043. As can be seen from Table 3 the this provides a more conservative 10-year survival estimate compared to no treatment waning but still within a

<table>
<tr><td></td><td></td><td>range that could be clinically plausible contrary to the ERGs waning assumption.</td></tr>
<tr><td>Key issue 10: Health-related quality of life – duration of utility benefits for nivolumab + ipilimumab</td><td>YES</td><td>Patient-reported outcomes measured in CM743 included the Lung Cancer Symptom Scale-Mesothelioma and EQ-5D-3L. Analyses of CM743 have showed that improvements in health-related quality of life for patients who received nivolumab + ipilimumab were maintained when compared with PDC (Scherpereel et al., 2020; Popat et al., 2021). In addition, symptom burden scores improved for patients who received nivolumab + ipilimumab compared with baseline versus a trend to deterioration for patients who received PDC. However, it is unclear whether these benefits will continue beyond the trial follow-up period.

We have explored additional scenarios of using treatment-dependent utilities until alternative time points other than 3 years. The resulting ICERs are presented below in Error! Reference source not found..

Table 4. Scenario analysis results exploring duration of treatment-dependent utilities
<table><tr><th>Scenario</th><th>ICER (£/QALY)</th></tr><tr><td>Treatment-dependent utilities until 3 years</td><td>£77,669</td></tr><tr><td>Treatment-dependent utilities until 5 years</td><td>£76,304</td></tr><tr><td>Treatment-dependent utilities until 7.5 years</td><td>£75,609</td></tr><tr><td>Treatment-dependent utilities until 10 years</td><td>£75,290</td></tr><tr><td>Treatment-dependent utilities over 20-year time horizon</td><td>£74,897</td></tr></table></td></tr>
<tr><td>Key issue 11: Resources and costs – estimation of time to treatment discontinuation</td><td>YES</td><td>As presented in the company submission, and the response to clarification questions, we maintain that the mean doses would be the best data source for estimation of treatment costs as it adequately reflects both treatment duration as well as dose intensity. The clinical expert consulted in preparation of this response also confirmed that he thought this would be representative of use in clinical practice.

Further, as presented in the company submission, the fit of standard parametric models to the trial data was poor. However, to meet the ERG’s request for parametric models to be included</td></tr>
</table>

		in the model further analyses has been undertaken so that a scenario can be presented with parametric distributions. To improve the fit of the parametric distributions for the nivolumab + ipilimumab arm survival analyses has been conducted per time to treatment discontinuation per nivolumab and ipilimumab treatment. In addition, spline models have been fitted to both the nivolumab, ipilimumab and PDC data to investigate if this would offer improved fit to the trial data. The full outcome of the survival analysis can be found in Appendix A. Based on the updated survival analysis splitting the analyses with nivolumab and ipilimumab specific survival analyses offer better fit to the data. For nivolumab of the standard distribution generalised gamma provide relatively good fit to the data. However, 1-knot spline hazard provides better visual fit and similar statistical fit and was therefore seen as a more appropriate distribution to use. For ipilimumab none of the standard distributions provide good visual fit to the data. Of the spline models both odds and hazard models provided reasonable visual and statistical fit while spline normal models did not converge. Of the spline hazard and odds models the 2-knots spline hazard model was deemed to provide the best fit to the data and therefore used in the analysis. For PDC visual fit of the spline models was relatively poor except for 3-knots spline odds and hazard models. Specifically, 3-knots spline models is needed to adequately capture the later part of the time to treatment discontinuation data for PDC (month 3-4) as both 1 and 2-knots models have a poor fit to the data. Thus, to allow for a scenario where the PDC arm time to treatment discontinuation is modelled with a parametric model the 3-knots hazards model was selected based on best visual and statistical fit to the data. In the scenario with parametric models fitted it should be noted that dose intensity has not been applied and thus would be likely to overestimate the number of doses received compared with clinical practice. Basing the time to treatment discontinuation on the parametric models instead of mean number of doses increased the revised base case ICER from £77,669

		to £78,803.
Key issue 12: resources and costs - uncertainty about subsequent treatments	**NO**	Per our response to Key Issue 4, there are currently no second-line therapies licensed for use in MPM. However, nivolumab monotherapy is being used in the NHSE in England under interim treatment options during the COVID-19 pandemic (NICE, 2021); 388 patients were treated with nivolumab monotherapy in this indication from August 2020 to April 2021. During technical engagement, the use of subsequent therapies was again validated with a UK clinician who noted that under the current guidance nivolumab monotherapy is the only approved treatment for patients who progress from PDC and, if reimbursed, patients receiving nivolumab + ipilimumab who progress would receive PDC. If nivolumab monotherapy is not available, vinorelbine is expected to be the next line of treatment following PDC. The clinician estimated that the average duration of second-line nivolumab monotherapy is 2 to 3 months, which aligns with the median duration of 84 days from the CONFIRM trial. The clinician estimated that the duration of second-line PDC following nivolumab + ipilimumab is 2.5 months, and vinorelbine following PDC is 2 months. We have performed a scenario analysis in which all patients who receive subsequent treatment after progressing from PDC get nivolumab monotherapy for a duration of 84 days and all patients who receive subsequent treatment after progressing from nivolumab + ipilimumab get PDC (66% carboplatin and 34% cisplatin) for a duration of 2.5 months. This scenario decreases the revised base case ICER from £77,669 to £75,552. An additional scenario without nivolumab monotherapy has been explored. All patients who receive subsequent treatment after progressing from PDC get vinorelbine for a duration of 1.7 months (aligning with the model base case) and all patients who receive subsequent treatment after progressing from nivolumab + ipilimumab get PDC (66% carboplatin and 34% cisplatin) for a duration of 2.5 months. This scenario increases the revised base case ICER from £77,669 to £81,522. However, as noted in response to Key Issue 4, initial assessment of adjusting for subsequent immunotherapy following PDC indicates that in this scenario the treatment effect for nivolumab + ipilimumab will improve and thus the ICER will decrease.

<table>
<tr>
<td>Key issue 13: Resources and costs – adverse events</td>
<td>NO</td>
<td>
Due to the very low incidence of these events and small differences between treatment arms, the impact to the ICER will be minor. The difference in adverse event costs in the base case analysis accounts for approximately 1% of the total incremental costs. Utility decrements for adverse events are not applied in the base case analysis that uses treatment-dependent utilities (to avoid double-counting).
We have run a scenario to estimate the impact on the ICER using a 1% cut-off for the inclusion of grade 3+ adverse events. We identified all additional adverse events that would be included with a 1% cut-off from CM-743 supplementary table S.6.4.2. The incidence of each adverse event for nivolumab + ipilimumab and PDC is presented below in Table 5.

Table 5. Incidence of additional grade 3+ drug-related adverse events for nivolumab + ipilimumab and PDC with a 1% cut-off from CM-743
<table>
<tr><th></th><th>Nivolumab + Ipilimumab</th><th></th></tr>
<tr><th>Grade 3+ AE</th><th>Incidence</th><th>PDC Incidence</th></tr>
<tr><td>Pruritus</td><td>1.0%</td><td>0.0%</td></tr>
<tr><td>Rash</td><td>1.3%</td><td>0.0%</td></tr>
<tr><td>Fatigue</td><td>1.0%</td><td>1.8%</td></tr>
<tr><td>Alanine aminotransferase increased</td><td>1.7%</td><td>0.7%</td></tr>
<tr><td>Aspartate aminotransferase increased</td><td>1.0%</td><td>0.4%</td></tr>
<tr><td>Hypopituitarism</td><td>1.0%</td><td>0.0%</td></tr>
<tr><td>Infusion related reaction</td><td>1.0%</td><td>0.7%</td></tr>
<tr><td>Pneumonitis</td><td>1.0%</td><td>0.0%</td></tr>
<tr><td>Hepatic function abnormal</td><td>1.7%</td><td>0.7%</td></tr>
<tr><td>Immune-mediated hepatitis</td><td>1.0%</td><td>0.0%</td></tr>
<tr><td>Drug-induced liver injury</td><td>1.0%</td><td>0.4%</td></tr>
</table>
</td>
</tr>
</table>

		<table><tr><td>Hepatitis</td><td>1.0%</td><td>0.0%</td></tr><tr><td>Febrile neutropenia</td><td>0.0%</td><td>1.1%</td></tr><tr><td>Pancytopenia</td><td>0.0%</td><td>1.8%</td></tr><tr><td>Acute kidney injury</td><td>1.3%</td><td>0.0%</td></tr><tr><td>Total</td><td>15.0%</td><td>7.6%</td></tr></table> The difference in total incidence of 7.4% and mean adverse event cost of £1,277.76 (calculated from the existing adverse event costs in the model) was applied to calculate an additional cost of £94.55 for nivolumab + ipilimumab. This increased the revised base case ICER from £77,669 to £77,810.
Key issue 14: Company's cost effectiveness results – proportion of progression-free life years (PF LYs) accumulated beyond the observed data	**NO**	A partitioned survival model approach was used with PF LYs generated directly from the PFS curves for nivolumab + ipilimumab and PDC (calculated using the area under the curves). Justification for the selection of PFS survival models and validation of the long-term extrapolations has been provided in response to clarification questions. A large proportion of the PF LYs are gained beyond the observed data period for nivolumab + ipilimumab compared with PDC. This occurs because PFS for PDC is initially higher than PFS for nivolumab + ipilimumab (a pattern of initially poor PFS followed by longer-term PFS benefits for patients who respond well to immunotherapy has been seen across different indications). In the company base case analysis PFS is higher for PDC until the curves cross in model cycle number 42 (9.7 months), from which point PFS remains higher for nivolumab + ipilimumab. Consequently, cumulative PF LYs are higher for PDC until model cycle 92 (21.2 months). Therefore, incremental PF LYs are positive for nivolumab + ipilimumab from 21.2 months and most of the total benefit is generated beyond the observed data period.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key Issue(s) in the ERG Report that the Change Relates to	Company's Base Case Before Technical Engagement	Change(s) Made in Response to Technical Engagement	Impact on the Company's Base-Case ICER
Original Base case			**77,531**
	'academic/commercial in confidence information removed'		
Key issue 9: Treatment effectiveness and extrapolation – immaturity of the long-term progression-free survival (PFS) and overall survival (OS) data	Extrapolation of PDC survival Original company preferred OS extrapolation was hybrid log-logistic for nivolumab + ipilimumab and hybrid exponential for PDC	Following the ERG response and further clinical input on survival extrapolations log-logistic without hybrid modelling has been selected for the nivolumab + ipilimumab arm and spline 2-knots normal for the PDC arm	74,897 'academic/commercial in confidence information removed'
Key issue 10: Health-related quality of life – duration of utility benefits for nivolumab + ipilimumab	Treatment-dependent utility values were applied for the full duration of the analysis	Following the ERG response treatment independent utility values have been applied from Year 3 and onward	76,732 'academic/commercial in confidence information removed'
Company's preferred base case following technical engagement		Based on the response provided above the following changes have been incorporated into the company's base case: • 'academic/commercial in confidence information removed' • 2 knots spline normal distribution for extrapolation of PDC OS • Treatment independent utility values applied from Year 3	77,669 'academic/commercial in confidence information removed'

References

Baas P, Daumont MJ, Lacoin L, Penrod J, Carroll R, Tanna N. Treatment patterns and outcomes in malignant pleural mesothelioma in England: a nationwide CAS registry analysis from the I-O Optimise initiative [poster 1909P]. Presented at the European Society for Medical Oncology Virtual Congress; 19-21 September 2020.

Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet. 2021 Jan 30;397(10272):375-86.

Bristol Myers Squibb (BMS). Efficacy and safety data to support flat dosing of nivolumab in mesothelioma subjects. BMS936558. 14 August 2020.

EMA. OPDIVO SmPC. OPDIVO (nivolumab) summary of product characteristics. Bristol Myers Squibb; 2020. Available at: Opdivo, INN-nivolumab (europa.eu). Accessed 14 May 2021.

Fennel D, Ottensmeier C, Califano R, Hanna GG, Weings S, Hill K, et al. Nivolumab versus placebo in relapsed malignant mesothelioma: Preliminary results from the CONFIRM Phase 3 Trial. Presented at the 2020 World Conference on Lung Cancer Singapore. January 28-31, 2021. Worldwide Virtual Event.

NICE. Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy. TA490. 22 November 2017. Available at: https://www.nice.org.uk/guidance/ta490/history. Accessed 14 May 2021.

NICE. NHS England interim treatment options during the COVID-19 pandemic. NG161. Available at: https://www.nice.org.uk/guidance/ng161/resources/interim-treatment-change-options-during-the-covid19-pandemic-endorsed-by-nhs-england-pdf-8715724381. Accessed 14 May 2021.

NICE. Nivolumab for treating advanced (unresectable or metastatic) melanoma. TA384. 18 February 2016. Available at: https://www.nice.org.uk/guidance/ta384. Accessed 14 May 2021.

NICE. Nivolumab in combination with ipilimumab for treating advanced melanoma. TA400. 27 July 2016. Available at: https://www.nice.org.uk/guidance/ta400. Accessed 14 May 2021.

NICE. Pembrolizumab for advanced melanoma not previously treated with ipilimumab. TA366. 25 November 2015. Available at: https://www.nice.org.uk/guidance/ta366. Accessed 14 May 2021.

NICE. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab. TA357. 07 October 2015. Available at: https://www.nice.org.uk/guidance/ta357. Accessed 14 May 2021.

NICE. Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease. TA558. 23 January 2019. Available at: https://www.nice.org.uk/guidance/ta558. Accessed 14 May 2021.

NICE. Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence. TA553. 19 December 2018. Available at: https://www.nice.org.uk/guidance/ta553 Accessed 14 May 2021.

Popat S, Scherpereel A, Antonia S, Oulkhouir Y, Bautista Y, Cornelissen R, Greillier L, et al. First-Line Nivolumab Plus Ipilimumab Versus Chemotherapy in Unresectable Malignant Pleural Mesothelioma (MPM) in CheckMate 743. iMig MS02:08 7 May 2021. Available at: https://imig2021.org/wp-content/uploads/2021/05/imig2021_Virtual_programmebook.pdf.

Scherpereel A, Antonia S, Bautista Y, Grossi F, Kowalski D, Zalcman G et al. First-line nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) for the treatment of unresectable malignant pleural mesothelioma (MPM): Patient-reported outcomes (PROs) from CheckMate 743. ESMO LBA1 1 December 2020. Available at: https://www.annalsofoncology.org/article/S0923-7534(20)43159-X/fulltext

Appendix A

Updated survival analyses of CheckMate-743 time to treatment discontinuation data

‘academic/commercial in confidence information removed’

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Thursday 15 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with untreated unresectable malignant pleural mesothelioma and current treatment options	
About you	
1. Your name	**Professor Richard Attanoos**
2. Name of organisation	**Representative for Royal College of Pathologists**
3. Job title or position	**Professor , Cardiff University** Consultant Pathologist, University Hospital of Wales
4. Are you (please tick all that apply):	☐ **x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **x** a specialist in the treatment of people with untreated unresectable malignant pleural mesothelioma? ☐ a specialist in the clinical evidence base for untreated unresectable malignant pleural mesothelioma or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ **x** yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**
The aim of treatment for untreated unresectable malignant pleural mesothelioma	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	As an expert pathologist this is outside my area of expertise.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	As an expert pathologist this is outside my area of expertise.

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in untreated unresectable malignant pleural mesothelioma?	YES
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	As an expert pathologist this is outside my area of expertise.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes – BTS mesothelioma guidelines. For pathology – RCPath Guidelines for Reporting Mesothelioma. ICCR Guidelines for Reporting Mesothelioma
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	As an expert pathologist this is outside my area of expertise.

• What impact would the technology have on the current pathway of care?	As an expert pathologist this is outside my area of expertise.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	As an expert pathologist this is outside my area of expertise.
• How does healthcare resource use differ between the technology and current care?	As an expert pathologist this is outside my area of expertise.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	As an expert pathologist this is outside my area of expertise.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As an expert pathologist this is outside my area of expertise. From a pathology laboratory perspective - none
13. Do you expect the technology to provide clinically meaningful	Yes

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As an expert pathologist this is outside my area of expertise.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	As an expert pathologist this is outside my area of expertise.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As an expert pathologist this is outside my area of expertise. Froma pathology laboratory perspective - none
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	As an expert pathologist this is outside my area of expertise.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	As an expert pathologist this is outside my area of expertise.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, I believe it is
• Does the use of the technology address any particular unmet need of the patient population?	Most beneficial for non-epithelioid mesothelioma
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As an expert pathologist this is outside my area of expertise.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	As an expert pathologist this is outside my area of expertise.
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	As an expert pathologist this is outside my area of expertise.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	As an expert pathologist this is outside my area of expertise.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	As an expert pathologist this is outside my area of expertise.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	As an expert pathologist this is outside my area of expertise.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance on pemexetred [TA135]?	As an expert pathologist this is outside my area of expertise.

23. How do data on real-world experience compare with the trial data?	As an expert pathologist this is outside my area of expertise.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	As an expert pathologist this is outside my area of expertise.
24b. Consider whether these issues are different from issues with current care and why.	As an expert pathologist this is outside my area of expertise.
Topic-specific questions	
25. Is railtrexed considered to be established clinical practice in the NHS for treating untreated unresectable malignant pleural mesothelioma?	As an expert pathologist this is outside my area of expertise.

26. Is best supportive care considered to be established clinical practice in the NHS for treating untreated unresectable malignant pleural mesothelioma with ECOG PS (Eastern Cooperative Oncology Group performance status) 0-1?	As an expert pathologist this is outside my area of expertise.
27. Is pemetrexed plus cisplatin or carboplatin considered to be established clinical practice in the NHS for treating untreated unresectable malignant pleural mesothelioma? What is the proportion of patients having pemtrexed plus cisplatin, or having pemtrexed plus carboplatin, respectively?	Yes - As an expert pathologist this is outside my area of expertise.

PART 2 – Technical engagement issues for clinical expert comment	
Issues arising from technical engagement	
We welcome your comments on the issues below, but you do not have to comment on every issue. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Effectiveness and safety of expected nivolumab fixed dosing: the effect of fixed/flat dosing (360mg every 3 weeks) aligning with anticipated EMA license vs. the weight-based dosing (3mg/kg every 2 weeks for up to 2 years) as used in CheckMate-743, is uncertain.	As an expert pathologist this is outside my area of expertise.
Key issue 2: Applicability of comparator to English NHS practice: the extent to which the clinical judgments made as to investigator choice of platinum doublet chemotherapy (PDC), i.e. carboplatin (67%) or cisplatin (33%) in CheckMate-743 match those that would be made in English NHS practice is uncertain.	As an expert pathologist this is outside my area of expertise.

Key issue 3: Immaturity of CheckMate-743 trial outcomes: the only results that have been presented are for an interim analysis with a database lock 3 April 2020.	As an expert pathologist this is outside my area of expertise.
Key issue 4: Subsequent therapy: there is a difference in the number of patients taking each type of subsequent therapy between the nivolumab plus ipilimumab and PDC arms of CheckMate-743 and, apparently, between the PDC arm and UK clinical experience.	As an expert pathologist this is outside my area of expertise.
Key issue 5: Subgroup effectiveness of nivolumab plus ipilimumab vs. PDC according to PD-L1 status and histology reveals potential variation and, in some cases, confidence intervals that overlap the point of no difference for both overall survival (OS) and progression-free survival (PFS).	As an expert pathologist this is outside my area of expertise.
Key issue 6: Model structure - the use of a partitioned survival model (PSM), without a state transition model (STM) approach to verify the results	As an expert pathologist this is outside my area of expertise.
Key issue 7: Population – no cost effectiveness analyses presented by histologic subtype (epithelioid, sarcomatoid, biphasic) or level of PD-L1 expression.	As an expert pathologist this is outside my area of expertise.

Key issue 8: Intervention & comparators – two-year stopping rule may not be completely adhered to in trial or in clinical practice.	As an expert pathologist this is outside my area of expertise.
Key issue 9: Treatment effectiveness and extrapolation – immaturity of the long-term PFS and OS data and the plausibility of assuming a continued treatment effect over the lifetime horizon of the model (i.e. no treatment effect waning).	As an expert pathologist this is outside my area of expertise.
Key issue 10: Health-related quality of life –duration of utility benefits for nivolumab + ipilimumab, the plausibility of maintenance of utility benefits over a lifetime horizon.	As an expert pathologist this is outside my area of expertise.
Key issue 11: Resources and costs – calculation of treatment costs and estimation of time to treatment discontinuation: using mean number of doses as reported in CheckMate-743 or, using dose intensity and parametric survival analysis based on time-to-treatment discontinuation data from the trial, to estimate time on treatment in the model.	As an expert pathologist this is outside my area of expertise.
Key issue 12: Resources and costs - uncertainty about subsequent treatments including proportion of patients on each arm using subsequent treatments, the mix of treatments used and duration of subsequent treatments: what proportion of patients receiving nivolumab plus ipilimumab	As an expert pathologist this is outside my area of expertise.

would have subsequent treatments compared with those receiving pemetrexed plus cisplatin or carboplatin, and for how long, respectively?	
Key issue 13: Resources and costs – adverse events: the exclusion of many adverse events from the model may introduce bias in favour of nivolumab plus ipilimumab	As an expert pathologist this is outside my area of expertise.
Key issue 14: Company's cost effectiveness results – proportion of progression-free life years (PF LYs) accumulated beyond the observed data is larger for nivolumab plus ipilimumab than for PDC.	As an expert pathologist this is outside my area of expertise.
Are there any important issues that have been missed in ERG report?	No
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement: • Immunotherapy is a key novel treatment for the management of malignant pleural mesothelioma • Immunotherapy with nivolumab and ipilimumab offers particular survival benefits for patients with non-epithelioid mesothelioma, which are usually associated with particularly adverse outcomes and have limited treatment options • As an expert pathologist much of the treatment related matters are outside my area of expertise. • From a pathology laboratory perspective there are no additional costs •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Thursday 13 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with untreated unresectable malignant pleural mesothelioma and current treatment options	
About you	
1.Your name	Richard Lech
2. Are you (please tick all that apply):	☒ a patient with untreated unresectable malignant pleural mesothelioma? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with untreated unresectable malignant pleural mesothelioma? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Mesothelioma UK
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement

	☒ I agree with it and **will be** completing this statement
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with untreated unresectable malignant pleural mesothelioma? If you are a carer (for someone with untreated unresectable malignant pleural mesothelioma) please share your experience of caring for them.	I was diagnosed with mesothelioma in February 2021 after having suffered some ill health 3-4 months previous. 12 months prior I had a substantial pleural effusion for which the biopsy showed no sign of cancer so I was not totally surprised to find that 12 months later I was finally diagnosed with mesothelioma. My attitude now is that it is a battle between the mesothelioma, my attitude and immunotherapy treatment. I'm a generally positive sort of person and very little makes me not positive and that includes this mesothelioma, so whilst physically I am getting weaker, mentally I am no less strong. It is too early to say whether the treatments are being effective as its less than 3 months since starting. The two CT scans since my February scan which found the mesothelioma have both shown no increase in the size of the cancer.

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for untreated unresectable malignant pleural mesothelioma on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I have no experience of other treatments available on the NHS.
8. If there are disadvantages for patients of **current NHS treatments** for untreated unresectable malignant pleural mesothelioma (for example how the treatment is given or taken, side effects of treatment etc) please describe these	I have no experience of other treatments available on the NHS.
Advantages of this treatment	
9a. If there are advantages of nivolumab plus ipilimumab over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others?	I have had no other treatments other than nivo and ipi but the advantage of being offered immunotherapy over other treatments under the EAMs scheme gave me a great source of immediate comfort following my diagnosis. Receiving nivo and ipi is giving me hope that I may still be here longer than the 6-9 months which historically seems to be the figures used for people with mesothelioma especially as the course of treatment lasts two years.

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does nivolumab with ipilimumab help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	I have no experience of other treatments available on the NHS.
Disadvantages of this treatment	
10. If there are disadvantages of nivolumab with ipilimumab over current treatments on the NHS please describe these? For example, are there any risks with nivolumab with ipilimumab? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	I have no experience of other treatments available on the NHS. The list of side effects handed out by my oncologist at our first meeting are frightening and my immediate thought is that I'm not putting those into my body, but of course, that's the list of side effects across a broad range of sufferers. My oncologist told me that the likelihood of any side effects appearing would be about 3 months after commencement of treatment. To date all of my side effects have been minor and has not altered my day-to-day life, so I don't know if I've been lucky and have no side effects of any significance or, in fact, am about to suffer a raft of them.
Patient population	
11. Are there any groups of patients who might benefit more from nivolumab with ipilimumab or any	New sufferers are probably aware of chemo and of its side effects which are well known and in some respects frightening. However, if they are offered nivo and ipi, I think that fear dissipates, and they become optimistic when optimism is required in their lives.

who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
Equality	
12. Are there any potential equality issues that should be taken into account when considering untreated unresected malignant pleural mesothelioma and nivolumab with ipilimumab? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	I am not aware of any equality issues.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	The committee should consider the increase in hope, even though it may be marginal, of the benefit that ipi and nivo would give sufferers.

PART 2 – Technical engagement issues for patient expert comment
Issues arising from technical engagement
We welcome your comments on the issues below, but you do not have to comment on every issue. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Are the comparators (the current treatment available in the NHS) in the company submission (pemexetred with cisplatin or pemexetred with carboplatin) used in the NHS for treating the condition?	
What are the main benefits of nivolumab with ipilimumab for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured?	
What are the benefits of nivolumab with ipilimumab for carers?	
Key issue 1: Effectiveness and safety of expected nivolumab fixed dosing: the effect of fixed/flat dosing (360mg every 3 weeks) aligning with anticipated EMA license vs. the weight-based dosing (3mg/kg every 2	

weeks for up to 2 years) as used in CheckMate-743, is uncertain.	
Key issue 2: Applicability of comparator to English NHS practice: the extent to which the clinical judgments made as to investigator choice of platinum doublet chemotherapy (PDC), i.e. carboplatin (67%) or cisplatin (33%) in CheckMate-743 match those that would be made in English NHS practice is uncertain.	
Key issue 3: Immaturity of CheckMate-743 trial outcomes: the only results that have been presented are for an interim analysis with a database lock 3 April 2020.	
Key issue 4: Subsequent therapy: there is a difference in the number of patients taking each type of subsequent therapy between the nivolumab plus ipilimumab and PDC arms of CheckMate-743 and, apparently, between the PDC arm and UK clinical experience.	
Key issue 5: Subgroup effectiveness of nivolumab plus ipilimumab vs. PDC according to PD-L1 status and	

histology reveals potential variation and, in some cases, confidence intervals that overlap the point of no difference for both overall survival (OS) and progression-free survival (PFS).	
Key issue 6: Model structure - the use of a partitioned survival model (PSM), without a state transition model (STM) approach to verify the results	
Key issue 7: Population – no cost effectiveness analyses presented by histologic subtype (epithelioid, sarcomatoid, biphasic) or level of PD-L1 expression.	
Key issue 8: Intervention & comparators – two-year stopping rule may not be completely adhered to in trial or in clinical practice.	
Key issue 9: Treatment effectiveness and extrapolation – immaturity of the long-term PFS and OS data and the plausibility of assuming a continued treatment effect over the lifetime horizon of the model (i.e. no treatment effect waning).	

Key issue 10: Health-related quality of life –duration of utility benefits for nivolumab + ipilimumab, the plausibility of maintenance of utility benefits over a lifetime horizon.	
Key issue 11: Resources and costs – calculation of treatment costs and estimation of time to treatment discontinuation: using mean number of doses as reported in CheckMate-743 or, using dose intensity and parametric survival analysis based on time-to-treatment discontinuation data from the trial, to estimate time on treatment in the model.	
Key issue 12: Resources and costs - uncertainty about subsequent treatments including proportion of patients on each arm using subsequent treatments, the mix of treatments used and duration of subsequent treatments: what proportion of patients receiving nivolumab plus ipilimumab would have subsequent treatments compared with those receiving pemetrexed plus cisplatin or carboplatin, and for how long, respectively?	

Key issue 13: Resources and costs – adverse events: the exclusion of many adverse events from the model may introduce bias in favour of nivolumab plus ipilimumab	
Key issue 14: Company's cost effectiveness results – proportion of progression-free life years (PF LYs) accumulated beyond the observed data is larger for nivolumab plus ipilimumab than for PDC.	
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Thursday 15 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with untreated unresectable malignant pleural mesothelioma and current treatment options	
About you	
1. Your name	**Dr Toby Laurence James Talbot**
2. Name of organisation	**Royal Cornwall Hospitals NHS Trust**
3. Job title or position	**Consultant Clinical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with untreated unresectable malignant pleural mesothelioma? ☐ a specialist in the clinical evidence base for untreated unresectable malignant pleural mesothelioma or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for untreated unresectable malignant pleural mesothelioma	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	There are always several aims of treatment for any patient with malignant disease including enhancement of prognosis, however, in my opinion the first and most important aim is to improve quality of life by reducing the symptom burden caused by the disease. This is particularly relevant in the treatment of malignant mesothelioma which frequently causes increasingly severe symptoms, particularly pain and breathlessness as the disease progresses. The primary endpoint in the Checkmate743 trial was overall survival.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity	In keeping with the above answer, the most clinically important aspect of response is in reduction of symptom burden and by extension, improved quality of life. Radiological assessment of response in mesothelioma is particularly challenging and as is often the case with immunotherapy agents/checkpoint inhibitors, radiological assessments can sometimes be misleading (lack of radiological response does not necessarily indicate lack of benefit from treatment).

by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in untreated unresectable malignant pleural mesothelioma?	Yes. Mesothelioma is a disease with a very poor prognosis compared to many other malignancies and further to this, as disease progresses, quality of life often deteriorates precipitously. There have been very few developments in systemic therapy for this disease in the last decade – the most commonly used chemotherapy combination (platinum-Pemetrexed) have been in use since 2008 (NICE TA135) and at that time was then biggest advance in treatment of mesothelioma with a three month survival advantage seen in the clinical trial which reported in 2003. Few clinical trials have shown any meaningful survival gain since then.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Virtually all patients with mesothelioma have inoperable disease and this disease is considered incurable outside of very rare, highly selected cases. Treatment is therefore palliative and aims to improve quality of life and prognosis. Patients with a good performance status (WHO 0 or 1) are most likely to be treated with systemic therapy using the approved agents of platinum (either cisplatin or carboplatin) with Pemetrexed. This is given intravenously on a 21 day cycle and up to six cycles are given dependant on response and tolerance. Patients with reduced performance status or not suitable for chemotherapy are managed with best supportive (palliative) care.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The British Thoracic Society (BTS) published guidelines for the investigation and management of mesothelioma in March 2018 (Woolhouse I, et al. Thorax 2018;73:i1-i30. Doi:10.1136/thoraxjnl-2017-211321) The European Society of Medical Oncology (ESO) published guidelines for the management of mesothelioma in 2020 (Scherpereel A, et al. European Respiratory Journal 2020; Doi: 101183/13993003.00953-29019)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is	Treatment pathways are well established and I do not believe there to be much variation in approach across the UK broadly speaking. Some difference of opinion exists between professionals when considering the benefits or otherwise in starting patients on systemic therapy at the earliest available opportunity or entering patients with low volume disease, low symptom burden or slowly progressing disease on active surveillance and reserving treatment for significant progression. There is variation in the selection of platinum agent – most oncologists will use carboplatin rather than cisplatin due to reduced infusion times and favourable toxicity profile, however, the original clinical trial used cisplatin exclusively and some believe that there may be higher activity with this platinum agent.

from outside England.)	
• What impact would the technology have on the current pathway of care?	I suspect that there will be no change in the philosophical arguments regarding immediate treatment versus active surveillance. If implemented, this technology would become standard of care as first line systemic therapy for mesothelioma in place of the currently used chemotherapy agents.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	There are similarities and differences between the technology (Ipilimumab and Nivolumab) and current therapy (platinum agent with Pemetrexed). Both are given intravenously on a 21 day cycle, almost universally in the outpatient setting. The infusion times for Ipilimumab-Nivolumab are considerably shorter than with chemotherapy and few, if any, supportive medications are required (eg antiemetics). Chemotherapy is typically limited to six cycles in total whereas Ipilimumab and Nivolumab are given for up to two years.
• How does healthcare resource use differ between the technology and current care?	As above – there are potential differences in the overall duration of treatment with Ipilimumab and Nivolumab given for up to 2 years and chemotherapy given for up to six cycles (typically 18 weeks). Chemotherapy, particularly cisplatin, can be resource intensive with pre and post treatment hydration schedules leading to total treatment time (chair time) of between six and eight hours per cycle. Ipilimumab and Nivolumab in combination are infused over sixty minutes and Nivolumab (given as single agent on alternate cycles) takes thirty minutes, so an average of 45 minutes per cycle. Premedication is required for Pemetrexed including vitamin B12 injections, oral folic acid and dexamethasone plus supportive medication such as ondansetron as anti-emetics. Immunotherapy can be of reduced toxicity compared to cytotoxic chemotherapy meaning that intensity of outpatient reviews (pre-treatment) may be reduced. The toxicity profile of immunotherapy would suggest that acute admission and utilisation of inpatient resources would be reduced compared to chemotherapy.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Ipilimumab and Nivolumab are classified as systemic anticancer therapy (SACT) so treatment needs to be supervised by appropriately trained oncologists and delivered by SACT trained nurses. Typically in the UK this would be through specialist clinics and treatment delivery units. This may change in the future if the classification changes to allow non-specialist unit delivery in which case, community delivery (eg in health centres, community hospitals etc) may be feasible.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or	Ipilimumab and Nivolumab (along with several similar immune checkpoint inhibitors) are in widespread use in the UK and no special additional investment should be required for its implementation for mesothelioma. Basic training may be required to familiarise the relevant teams to the treatment protocol specifics.

training.)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The initial data release from the Checkmate743 clinical trial relating to this technology (Ipilimumab and Nivolumab vs carboplatin and Pemetrexed) showed a significant overall survival gain of four months in the intention to treat (ITT) group – as far as I am aware, this is the largest survival gain ever seen with systemic therapy in mesothelioma. The proportion of patients alive at 2 years from randomisation was 41% in the immunotherapy compared to 27% in the control arm (chemotherapy). The toxicity profile of immunotherapy is better than with chemotherapy so it is anticipated that patients will experience fewer side effects with this technology.
• Do you expect the technology to increase length of life more than current care?	Yes. As above, the initial data read out from the Checkmate743 trial confirms a significant median survival benefit of 4 months (ITT group) with compelling further survival gain seen in some subgroups according to subgroup analysis reported in the trial. It is now a recognised phenomenon that immune checkpoint inhibitors will often lead to very durable benefit for a subset of patients (the “tail on the curve” effect), The data from the Checkmate743 trial are too immature to draw conclusions about long term survival probability but in other tumour types, long term (beyond five years) survival can be seen in 15-20% of patients with surprising frequency.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Increased quality of life will be driven by better disease control leading to reduced symptom burden. Immune checkpoint inhibitors are typically better tolerated than cytotoxic chemotherapy so quality of life is expected to be improved whilst on treatment.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Perhaps. The Checkmate743 clinical trial formal data release, published in the Lancet in January 2021 (Baas P, et al. https://doi.org/10.1016/S0140-6736(20)32714-8) included analysis of some subgroups. Mesothelioma can be broadly divided into two broad groups based on histopathological assessment – these are “epithelioid” and “non-epithelioid” subtypes. “Non-epithelioid” incudes patients with sarcomatoid and mixed/biphasic disease. Approximately 75% of mesothelioma diagnoses are that of epithelioid subtype with the remainder non-epithelial by definition. It is known that non-epithelioid, particularly sarcomatoid subtypes carry a particularly poor prognosis and that this is driven by low likelihood of response to chemotherapy and generally more biologically aggressive disease. Subgroup analysis in the trial showed an apparent increased benefit of immunotherapy over chemotherapy in the non-epithelioid group and a marked overall survival gain in this group of around 10 months. By comparison, the survival gain in the larger epithelial group is smaller with a gain of just under two months. Caution is required when interpreting subgroup analyses in any randomised clinical trial as, by definition, the numbers of patients included in statistical analysis is reduced compared to the ITT group which reduces the power of the study to detect meaningful differences. It is understood in oncology that when considering subgroup analyses from clinical trials is that such data should inform

	clinical trial design, but not treatment decision making. The trial also included subgroup analysis based on PDL1 expression in the tumours with an apparent survival advantage seen in patients whose tumours express PDL1 at a level of >1%. PDL1 is not routinely analysed in mesothelioma in the UK so I am unable to comment how this may be applicable to our population other than to refer back to the above comments on subgroup analyses.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	In my opinion, this technology would be considerably easier for patients to use based on my personal experience with Ipilimumab and Nivolumab – patients usually experience far fewer side effects with this treatment compared to conventional chemotherapy. It needs to be noted that the maximum duration of treatment with Ipilimumab and Nivolumab is two years and this requires repeated visits to treatment units rather than only a few for chemotherapy so in this respect, there may be an additional burden on patients and their families. I would not anticipate a meaningful change in the numbers of clinic appointments, CT scans or other investigations such as blood tests.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I would anticipate that the recommended dosing schedule for Ipilimumab and Nivolumab will be in line with the current Expanded Access to Medicine Scheme (EAMS) with 21 day cycles with both drugs on one cycle alternating with monotherapy Nivolumab for the next. Note that in the Checkmate743 trial, Nivolumab was given every 14 days – the posology for Nivolumab has been adjusted in line with pharmacokinetic data. Treatment is likely to be given until disease progression, toxicity that requires discontinuation or intolerance, or two years therapy has been achieved.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Perhaps. Mesothelioma is a disease strongly associated with asbestos exposure, usually through an occupational setting and exposure through working life. This means that it is classified as industrial disease which has legal implications as well as need for coronial investigation (inquest) after death. In my experience, patients with mesothelioma can feel as if the disease has been "done to them" and that if it had not been for their line of work then they would not have become terminally ill. This leads to a unique psychology with an anger against the disease that is not commonly seen in other cancers. Having effective treatment with favourable toxicity profile would help alleviate some of this emotion in my opinion – patients will often have a prejudicial view of chemotherapy and many will refuse it outright simply because it is "chemotherapy". I am not sure if QALY calculations would be able to take account of this complex disease associated psychology.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. This is the first treatment to show a meaningful survival advantage of any kind in over a decade and it is the first time that non-cytotoxic treatment has been shown to help in mesothelioma.
• Is the technology a 'step-change' in the management of the condition?	Yes – this is the biggest advance in mesothelioma in over a decade of research
• Does the use of the technology address any particular unmet need of	Yes – as above, many patients will decline the offer of chemotherapy simply due to it being chemotherapy. The presence of this technology as a treatment option will be more acceptable to greater patients meaning more will

the patient population?	benefit from prognosis and symptom enhancing treatment.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects of immunotherapy can be unpredictable and are driven by autoimmune phenomena. Checkpoint inhibitors are now in very widespread use in multiple tumour types and settings and therefore clinical awareness of the specific toxicities and management of them has improved markedly over recent years. Severe and potentially life threatening toxicity can occur and for those patients there is no doubt that quality of life would be eroded, however, in clinical practice and in my experience, the incidence of severe toxicity is much lower with immunotherapy than with chemotherapy. Most side effects from checkpoint inhibitors are fully reversible – the exception to this is in endocrine toxicity (most commonly hypothyroidism) which if seen, is usually permanent. This means that in those patients that experience endocrine toxicity then replacement therapy (eg thyroxine) is likely to be needed indefinitely with potential minor erosion of quality of life.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, I believe so. The control arm in Checkmate743 used carboplatin exclusively as the platinum agent and as discussed separately, carboplatin is the most frequently used platinum agent combined with Pemetrexed in UK practice.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival, standard statistical analysis. Quality of life measure are being reported separately (not published yet)

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No. Reported adverse events (side effects) in the Checkmate743 were entirely in keeping with my clinical experience.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance on pemexetred [TA135]?	Since 2008, platinum and Pemetrexed has been standard of care throughout the world in first line treatment of mesothelioma and therefore has formed the control arm for most studies exploring possible new therapies. Of these studies, the data published for patients receiving platinum-Pemetrexed is largely in line with the original clinical trial and real world experience. It should be noted that there has been a mix of cisplatin or carboplatin used as the platinum agent with Pemetrexed.
23. How do data on real-world experience compare with the trial	Real world use has come from use through the approved EAMS. The response and toxicity profile is very similar to that reported in the study.

data?	
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Perhaps. Mesothelioma is an industrial disease from occupational exposure to asbestos and therefore typically patients would be in lower socioeconomic groups compared to other cancer types. It has been long recognised that people from lower socioeconomic backgrounds experience health inequality and fare less well with most diseases including malignancy.
24b. Consider whether these issues are different from issues with current care and why.	This is not a new phenomenon and will not differ from current care.
Topic-specific questions	
25. Is railtrexed considered to be established clinical practice in the NHS for treating untreated unresectable malignant pleural mesothelioma?	No. I have never used Raltitrexed in the management of mesothelioma and I know of no oncologists in the UK that have used it.
26. Is best supportive care considered to be established clinical practice in the NHS for	Yes. Not every patient will want or be suitable for systemic therapy even if performance status would support it. For those patients, supportive (palliative) care would be the standard approach.

treating untreated unresectable malignant pleural mesothelioma with ECOG PS (Eastern Cooperative Oncology Group performance status) 0-1?	
27. Is pemetrexed plus cisplatin or carboplatin considered to be established clinical practice in the NHS for treating untreated unresectable malignant pleural mesothelioma? What is the proportion of patients having pemtrexed plus cisplatin, or having pemtrexed plus carboplatin, respectively?	I do not have precise figures on this but anecdotally, carboplatin is much more widely used than cisplatin in the UK despite the fact that in the original trial, cisplatin was used as the platinum agent with Pemetrexed and as single agent in the control arm. In my own practice I use carboplatin exclusively and have not used cisplatin for many years, mostly due to chair time and toxicity profile. There have been few head-to-head studies in any cancers comparing cisplatin with carboplatin but in those that have done (notably BTOG2 in non-small cell lung cancer) there have been no major advantages for one over the other in terms of response rates, survival gain and disease control. I would be very surprised if cisplatin made up more than 10% of platinum agents used in mesothelioma in the UK.

PART 2 – Technical engagement issues for clinical expert comment	
Issues arising from technical engagement	
We welcome your comments on the issues below, but you do not have to comment on every issue. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Effectiveness and safety of expected nivolumab fixed dosing: the effect of fixed/flat dosing (360mg every 3 weeks) aligning with anticipated EMA license vs. the weight-based dosing (3mg/kg every 2 weeks for up to 2 years) as used in CheckMate-743, is uncertain.	
Key issue 2: Applicability of comparator to English NHS practice: the extent to which the clinical judgments made as to investigator choice of platinum doublet chemotherapy (PDC), i.e. carboplatin (67%) or cisplatin (33%) in CheckMate-743 match those that would be made in English NHS practice is uncertain.	
Key issue 3: Immaturity of CheckMate-743 trial outcomes: the only results	

that have been presented are for an interim analysis with a database lock 3 April 2020.	
Key issue 4: Subsequent therapy: there is a difference in the number of patients taking each type of subsequent therapy between the nivolumab plus ipilimumab and PDC arms of CheckMate-743 and, apparently, between the PDC arm and UK clinical experience.	
Key issue 5: Subgroup effectiveness of nivolumab plus ipilimumab vs. PDC according to PD-L1 status and histology reveals potential variation and, in some cases, confidence intervals that overlap the point of no difference for both overall survival (OS) and progression-free survival (PFS).	
Key issue 6: Model structure - the use of a partitioned survival model (PSM), without a state transition model (STM) approach to verify the results	
Key issue 7: Population – no cost effectiveness analyses presented by histologic subtype (epithelioid, sarcomatoid, biphasic) or level of PD-L1 expression.	
Key issue 8: Intervention & comparators – two-year stopping rule may not be completely adhered to in trial or in clinical practice.	

Key issue 9: Treatment effectiveness and extrapolation – immaturity of the long-term PFS and OS data and the plausibility of assuming a continued treatment effect over the lifetime horizon of the model (i.e. no treatment effect waning).	
Key issue 10: Health-related quality of life –duration of utility benefits for nivolumab + ipilimumab, the plausibility of maintenance of utility benefits over a lifetime horizon.	
Key issue 11: Resources and costs – calculation of treatment costs and estimation of time to treatment discontinuation: using mean number of doses as reported in CheckMate-743 or, using dose intensity and parametric survival analysis based on time-to-treatment discontinuation data from the trial, to estimate time on treatment in the model.	
Key issue 12: Resources and costs - uncertainty about subsequent treatments including proportion of patients on each arm using subsequent treatments, the mix of treatments used and duration of subsequent treatments: what proportion of patients receiving nivolumab plus ipilimumab would have subsequent treatments compared with those receiving pemetrexed plus cisplatin or carboplatin, and for how long, respectively?	

Key issue 13: Resources and costs – adverse events: the exclusion of many adverse events from the model may introduce bias in favour of nivolumab plus ipilimumab	
Key issue 14: Company's cost effectiveness results – proportion of progression-free life years (PF LYs) accumulated beyond the observed data is larger for nivolumab plus ipilimumab than for PDC.	
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **Wednesday 19 May 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
  - Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Eleni Theodorou**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bristol Myers Squibb Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key Issue	Does This Response Contain New Evidence, Data Or Analyses ?	Response	ERG critique
Additional questions received on 12 May		The company has initiated work to assess the impact of switching from PDC to immunotherapy in the trial, after it was highlighted in an email received from NICE on 12th May 2021 that the impact on both OS and the ICER should be explored. Due to the limited time available, it has not been possible to conduct a full assessment for inclusion in this response. However, an initial assessment indicates that adjusting for immunotherapy following PDC will improve the treatment effect for nivolumab + ipilimumab and therefore reduce the ICERs. Regarding the differences between the rates of subsequent treatments reported in the CSR (table 6.5.3-1) and those that the company noted were used in the economic model (table 44 of the CS), the 9 most common subsequent treatments were included in the model. However, the total sum of all subsequent treatments was greater than 100%. A decision was made to reweight the proportion receiving each of the 9 included subsequent treatments to sum to 100%. Additionally, the CSR reports the proportion of the total arm (e.g. 41 out of 302 = 13.6%), however, the model used the proportion of those receiving subsequent	The ERG awaits the results of the additional analysis.

		systemic therapy, which was 123, making 123 the denominator.	
Key issue 1: Effectiveness and safety of expected nivolumab fixed dosing	**YES**	As noted in the company submission and response to clarification questions, the dosing and schedule of nivolumab in CheckMate-743 (3 mg/kg every 2 weeks) differs from the proposed indicated dose and schedule of nivolumab submitted to the European Medicines Agency (EMA) and included in the CHMP positive opinion (22 April, 2021; 360 mg every 3 weeks). Based on the totality of pharmacokinetic modelling of nivolumab exposure, exposure-efficacy, exposure-safety, and clinical subgroup efficacy and safety analyses, the balance of benefits and risks of nivolumab 360 mg Q3W is expected to be similar to that of nivolumab 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W for the treatment of untreated unresectable MPM.  	The company have provided no new evidence. As stated in the ERG report, “Subgroup analyses by weight were also provided, but again these do not show the effect of patients receiving a lower or higher dose, as would have been the case if dosing had been weight-based. Therefore, uncertainty remains regarding the effectiveness and safety of the expected licensed dose of nivolumab.” (p. 25)

		[redacted] The EMA has accepted a change from weight-based to flat dosing in a number of other nivolumab indications, including second-line NSCLC and cancer of the head and neck and this was not considered an issue when discussed during appraisal (TA490). After their rigorous assessment of the available data, the EMA accept that the flat dosing of nivolumab provides equivalent efficacy and safety to the weight-based dosing in trials, the SmPC states: "Based on modelling of dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between a nivolumab dose of 240 mg every 2 weeks or 3 mg/kg every 2 weeks. Additionally, based on these relationships, there were no clinically significant differences between a nivolumab dose of 480 mg every 4 weeks or 3 mg/kg every 2 weeks in adjuvant treatment of melanoma, advanced melanoma and advanced RCC" (EMA, 2021). Because the EMA's role is to ensure the efficacy and safety of medicines available in Europe, their recommendation should also inform NICE's assessment.	
Key issue 2: Applicability of comparator to English NHS practice	**NO**	The most relevant data on current treatment practice in the NHS in England come from the national Cancer Analysis System (CAS) registry that includes **all** patients newly diagnosed with MPM in England between January 2013 and December 2017 (Baas et al., 2020). Because no new treatments have been approved in MPM since December 2020, this analysis represents the best possible evidence for the current treatment pathway in England. Of the 2,810 patients who received first-line therapy with a platinum + pemetrexed, [redacted]	The percentages of patients who received each of carboplatin and cisplatin at randomisation in the CheckMate-743 trial do appear to be similar to those in the CAS registry. However, although the company assert that the CAS registry is the most relevant source, the ERG believe that this is

		[redacted] These data for all MPM patients treated with first-line chemotherapy in England are similar to those reported in the CheckMate-743 trial (Baas et al., 2021). After randomisation, 104 (34%) of 302 patients in the chemotherapy group were given cisplatin and 180 (60%) were given carboplatin; 29 (28%) of 104 patients given cisplatin switched to carboplatin after the first dose due to investigator decision. Therefore, overall, 74% of patients were treated with carboplatin and 37% with cisplatin.	questionable given that the data could be considered to be too old. As mentioned in the ERG report, the percentages in the more recent UK National Mesothelioma Audit 2020 appear to be quite different. The implications of this difference remain unknown.
Key issue 3: Immaturity of CheckMate-743 trial outcomes	**NO**	New data cuts of CheckMate-743 are planned in [redacted], if new analyses are available before the appraisal committee meeting, we will provide them as additional evidence.	The ERG await the results of the new analyses.
Key issue 4: Subsequent therapy: difference between arms and applicability to English NHS practice	**NO**	As provided in response to clarification questions, in CheckMate-743, after study treatment was discontinued, similar proportions of patients in each treatment arm received subsequent therapy: 44.2% of those treated with nivolumab + ipilimumab subjects and 40.7% of those treated with PDC (Baas et al., 2021). Most subjects received subsequent chemotherapy (43.2% and 31.5% from the nivolumab + ipilimumab and PDC arms, respectively). Subsequent immunotherapy (anti–PD-1/PD-L1, anti-CTLA-4, other) was received by 3.3% of the nivolumab + ipilimumab and 20.2% of the PDC arm, respectively. A small percentage of subjects received subsequent experimental therapies (0.7% and 4.0% in the nivolumab + ipilimumab and PDC arms, respectively). During technical engagement, a clinician was asked what percentage of patients receive subsequent therapy in England, he estimated 30% of PDC-treated patients and 35% of nivolumab + ipilimumab-treated patients would receive second line therapy.	The ERG awaits the results of the additional analysis.

		In CheckMate-743, more patients received subsequent immunotherapy after PDC than with nivolumab + ipilimumab, which is expected since use of a subsequent therapy with a different mode of action to prior treatment is standard clinical practice. Patients with MPM treated with second-line therapies have a short life expectancy, and therefore duration of subsequent treatments is also short. Real-world data from the CAS registry of patients with unresectable MPM in England from January 2013-December 2017 showed that median OS was 8.5 months from start of second-line therapy and median treatment duration of second-line therapy was 1.6 months (Baas et al., 2020). For the company submission, this assumption was validated by UK clinical experts. There are currently no second-line therapies licensed for use in MPM as no second-line therapy has shown a survival benefit in MPM in a randomised controlled trial with an active comparator. However, nivolumab monotherapy is being used in the NHSE in England under interim treatment options during the COVID-19 pandemic (NICE, 2021). Based on this interim guidance, from August 2020 to April 2021, 388 patients were treated with nivolumab monotherapy in this indication. Preliminary results of the phase 3 CONFIRM trial of nivolumab versus placebo in relapsed MPM confirm the registry data in terms of the duration of subsequent therapy (Fennell et al., 2021). The median duration of treatment was 84 days in the nivolumab arm (n = 221) and 43 days in the placebo arm (n = 111). During technical engagement, the durations of therapy were again validated with a UK clinician who noted that there are no subsequent therapies approved in the UK (other than nivolumab monotherapy due to COVID-19), but anticipated that those who received subsequent therapy would have it for between 1 and 3 months (approximately 1-2 months for gemcitabine, 2 months for vinorelbine, 2.5 months for	

		PDC, and 2-3 months for nivolumab monotherapy). Overall, the company considers that any confounding of OS due to subsequent treatments is likely to be biased in favour of the PDC arm, resulting in an underestimate of the incremental improvement in OS reported for nivolumab + ipilimumab. As noted earlier the company has initiated work to assess the impact of switching from PDC to immunotherapy in the trial. The initial assessment indicates that adjusting for immunotherapy following PDC will improve the treatment effect for nivolumab + ipilimumab.	
Key issue 5: Subgroup effectiveness of nivolumab + ipilimumab according to PD-L1 status and histology	**NO**	Patients with MPM have a poor prognosis with current treatments, with low 3-year survival rates of approximately 10% across all disease stages and histological subtypes. There is therefore a high unmet clinical need for all patients with MPM, regardless of histological subtype or level of PD-L1 expression. As stated in our response to clarification questions, evidence for the levels of PD-L1 expression in patients with MPM in England is inconsistent, with wide variation in the threshold cut-offs used and the rates of PD-L1 expression observed in clinical studies (see Table 3 in Document B, p17). As a result, large differences have been reported, with 20% to 70% of specimens tested being considered PD-L1–positive. Unlike other lung cancers in which PD-L1 inhibitors are already approved and PD-L1 testing is standard practice, PD-L1 testing is not routinely performed on biopsies from patients with MPM in the NHS in England, and the thresholds, scoring methods, and antibodies used to detect PD-L1 expression in MPM are not standardised which may contribute to this variation. Reliable PD-L1 testing is highly dependent on biopsy, which is technically difficult in MPM because MPM tumours have spatial heterogeneity and the amount of tissue obtained is usually not sufficient for accurate PD-L1 testing. For these reasons and	As stated in the ERG report, Table 1.6, “Subgroup analysis by both PD-L1 status and histology, which was included in the scope, reveals potential variation and in some cases 95% CIs that overlap the point of no difference for nivolumab + ipilimumab versus PDC for both OS and PFS. This is particularly the case for PD-L1<1% where for PFS there is little uncertainty (point estimate for HR greater than 1 and 95% CI does not include 1) that PDC is superior and for OS where there appears to be little difference between groups (95% CI includes 1).” Therefore, given this evidence and that subgroup analyses by PD-L1 status and histological subtype were specified in the scope, the ERG continues to recommend it be

		because until now no PD-L1 inhibitor has shown benefit in MPM in the first-line setting, PD-L1 testing is not currently a standard test in the NHS for this patient population (see clinical expert opinion: Appendix N of the company submission). PD-L1 was not a stratification factor in CheckMate-743; therefore, the data for PD-L1 subgroups are limited by potential imbalances in known or unknown prognostic factors and because the role of PD-L1 in MPM is unclear. Although the OS benefit with nivolumab + ipilimumab versus PDC was greater in patients with PD-L1 ≥ 1% (HR, 0.69; 95% CI, 0.55-0.87) than in patients with PD-L1 < 1% (HR, 0.94; 95% CI, 0.62-1.40). within the treatment group, similar OS was observed with nivolumab + ipilimumab regardless of PD-L1 expression (median OS of 17.3 months in PD-L1 < 1% and 18.0 months in PD-L1 ≥ 1%). Owing to the small sample size and event counts in the PD-L1–negative subgroup, the statistical analyses in the PD-L1 subgroups are descriptive in nature and should be interpreted with caution. In addition, due to the severe limitations in PD-L1 testing in MPM and the survival seen in both PD-L1 < 1% and ≥ 1% subgroups in CheckMate-743, the company does not consider patient selection criteria for nivolumab + ipilimumab by levels of PD-L1 expression as appropriate, given the high clinical unmet need and short life expectancy of all patients with unresectable MPM eligible for SACT. Histological subtype (epithelioid or non-epithelioid) was a stratification factor in CheckMate-743, as presented in the Company Submission, an OS benefit was observed in epithelioid and non-epithelioid subgroups, with similar median OS for nivolumab + ipilimumab in both histology subgroups. The treatment effect of nivolumab + ipilimumab versus PDC was more pronounced in the non-epithelioid subgroup (HR, 0.46) than in the epithelioid subgroup (HR, 0.86), driven by the known poorer performance of PDC in the non-epithelioid subgroup.	conducted for cost-effectiveness and assert that they are relevant for decision making.

		Nonetheless, there remain issues with histological typing in MPM, meaning subgroups should not be used in decision making in this indication. In clinical practice in the UK, a high proportion of patients with MPM have unknown or not otherwise specified (NOS) histology. Real-world data from the CAS registry in England from January 2013-December 2017 (Baas et al., 2020) showed that of 2,810 patients who received first-line pemetrexed + platinum-based therapy, 34.5% had histology that was not otherwise specified and 3.2% were unknown subtype. Reasons given for this by UK clinical experts were the technical difficulties with obtaining a biopsy in MPM and that histological subtype can be a broad spectrum that is hard to define (Company submission, Appendix N). For these reasons, the company considers the outcomes in the histological subgroups in CheckMate-743 as descriptive in nature and should be interpreted with caution. In addition, the company does not consider patient selection criteria for nivolumab + ipilimumab by histological subtype as appropriate, given the limitations in histological subtyping in real-life clinical practice; the significant OS benefit seen in both epithelioid and non-epithelioid subgroups in CheckMate-743 and the high clinical unmet need of all patients with unresectable MPM eligible for SACT. Because there are inherent issues in terms of subgroup analyses by both PD-L1 and histology, analyses that combine these two subgroups would be inappropriate, result in increased uncertainty and have not therefore been undertaken. Additional data cuts of CheckMate-743 are not yet available; BMS will be able to provide analyses from these as they become available. The use of subgroups in decision making was discussed with a clinical expert during technical engagement. The clinician considered that there is an unmet need for new treatments for all patients with MPM and	

		determining access to nivolumab + ipilimumab based on subgroups would exclude patients who would benefit from it – the level of OS benefit in the entire intention-to-treat population has never been seen in other studies in MPM. Furthermore, because CheckMate-743 was not powered for these subgroup analyses, differences in the efficacy results in subgroups may have been caused by chance. Therefore, while subgroup analyses are interesting, they are intended to drive further research and are not appropriate for use in clinical decision making.	
Key issue 6: Model structure - the use of a partitioned survival model (PSM), without a state transition model (STM) approach to verify the results	**NO**	As presented in the response to the ERG's clarification questions multiple model structures were considered during the development of the economic model, including state transition modelling. As presented in our previous response, a virtual European advisory board for the economic modelling of nivolumab + ipilimumab in 1L MPM was carried out in November 2020 and consisted of 12 experts across Europe, including 4 from the UK (one clinical oncologist, one clinical senior lecturer, one professor of medical statistics and one senior research fellow). Advisors agreed that partitioned survival models (PSM) were widely accepted by HTA bodies due to their straightforward approach and their use of data taken directly from the trials (OS and PFS); and most advisors agreed with a PSM being used for nivolumab + ipilimumab in 1L MPM. Therefore, based on data availability, input from health economic advisory boards and to be aligned with previous NICE cancer appraisals, a partitioned survival model was chosen. We would also like to point out that in the specific recommendation the ERG refers to for presenting a state transition model the DSU also concludes that state transition models cannot be recommended over partitioned survival models, given the need for further research around state transition models. Further, it is also pointed out that, although state transition models might have some benefits over partitioned survival models (given they model health state occupancy more explicitly), long-	The ERG broadly agrees with the company that there is limited evidence on the superiority of state transition models over partitioned survival models, but considers that validation of partitioned survival models using a different modelling approach is nevertheless desirable. Adhering to methodological guidance, as provided in the relevant NICE DSU, is essential in areas where methodological development is needed and there is no generally accepted or preferred approach. This determined the ERG´s preference to follow recommendations (NICE DSU TSD 19) and use state transition models alongside partitioned survival models to verify the plausibility of extrapolations and explore key clinical uncertainties in the

		term predictions are still dependent on the within-trial trends in individual transition rates being representative of post-trial trends. We are not aware of, and the ERG has not presented, evidence that shows that extrapolations from state transition models in general would provide more precise long-term extrapolations compared with partitioned survival models and thus address the ERGs comment about majority of results being generated beyond the trial follow up. On the contrary, the DSU highlight that methodological development is needed around how the model fit for state transition models should be assessed. This given that typical model outputs to which a good fit is expected (e.g., OS) is based on a composite of multiple fitted survival functions in a state transition model. Presenting a state transition model in addition to the submitted model would have required an unreasonable amount of work, including the need for clinical validation of all analyses resulting from such a model in addition to the partitioned survival model already presented.	extrapolation period. There remains uncertainty about the partitioned survival modelling approach, as detailed in the ERG report.
Key issue 7: Population – no subgroup cost effectiveness analyses presented	**NO**	As described in detail in response to Issue 5, there is an unmet need for effective treatments in all patients with MPM, and in CheckMate-743, efficacy benefits were seen in the entire intention-to-treat population. There are issues in terms of the assessment of both PD-L1 and histology in patients with MPM that mean they are unreliable, and analyses of combined subgroups would add further uncertainty. Therefore, decision making should be based on the entire population eligible for nivolumab + ipilimumab in this indication.	See response to Issue 5
Key issue 8: Intervention & comparators – two-year stopping rule	**NO**	In practice in the UK, the 24-month stopping rule is routinely used in multiple indications across IOs and information from NHSE in previous appraisals suggests that this is adhered to. We agree with the ERG that the 2 patients in CheckMate-743 who remained on therapy after 24 months will have minimal impact on model results, and based on	The remaining issue is uncertainty about why these patients did not adhere to the stopping rule and whether this could occur in clinical practice and to what extent. If so,

may not be completely adhered to in trial		NHSE input to previous appraisals, will not be an issue in clinical practice.	the stopping rule may need to be relaxed in the model (for a proportion of patients).

Key issue 9: Treatment effectiveness and extrapolation – immaturity of the long-term progression-free survival (PFS) and overall survival (OS) data	**YES**	**<u>Extrapolation of PDC OS</u>** With regards to the choice **of parametric** distribution for modelling of the PDC arm, as with the nivolumab + ipilimumab arm, a key selection criterion was the clinical plausibility of the long-term survival. We agree with the ERG that the log-logistic distribution provides clinically plausible survival predictions for nivolumab and ipilimumab. However, as presented in the company submission we do not agree that selection of the log-logistic distribution for PDC results in clinically plausible survival predictions. We agree that the hybrid approach originally selected has some areas of uncertainty as presented by the ERG and thus explored spline models per the ERG's request as part of the clarification questions. As presented in our response to the clarification questions, some of the spline models provided improved fit to the trial data compared with the standard parametric functions as well as clinically plausible long-term predictions. Given the improved within-trial fit of these models compared with the exponential model, while also providing clinically plausible long-term predictions they could be considered preferable to the exponential. Use of spline models would thereby negate the need for a piecewise model to be applied to improve fit for the within-trial period. Thus, scenarios without piecewise modelling for both arms were presented in our response to the clarification questions with spline 2 knots hazard, spline 1-knot normal, and 2-knots normal used for PDC. Since submission of our response to the clarification questions, further assessment and validation of the spline models has been conducted with input from a UK clinical expert. Based on this further validation an updated version of Table 1 in the company submission for PDC survival extrapolations is presented below.	The company state that they do not agree with the selection of the log-logistic model for the PDC arm, on the basis that this did not meet clinical plausibility criteria defined by experts (it did meet all other criteria), who expected 5-, 7.5- and 10-year survival to be at 5%, 2% and 0%. Indeed the log-logistic predicted 7.5% and 2.1% respectively for the 5- and 10-year time points. This was still an under-estimate compared with MAPS 5-year data (8.1%). Additionally, consistent with this comparison, the plausibility of the extrapolated survival for the log-logistic distribution was not considered unreasonable based on CS Table 32. The ERG therefore does not rule out the log-logistic as an appropriate model for OS in the PDC arm. The company provided a new base-case using the spline 2 knots normal model. This was chosen among a selection of spline models with 1 and 2 knots. The ERG welcomes this analysis. The company did not provide detail on

Table 1. Summary of Assessment of Selection Criteria for Distributions for PDC Overall Survival

Distribution	AIC	BIC	Over/under-estimates of median survival	Appropriate hazard function	Plausible survival predictions
Weibull	✓	✓	↑	✗	✗
Gamma	✓	✓	↑	✗	✗
Gompertz	✗	✗	↑	✗	✗
Generalised gamma	✓	✓	↑	-[a]	-
Exponential	✗	✗	↓	✗	✓
Log-logistic	✓	✓	↓	✓	✗
Log-normal	✗	✗	↓	✓	✗
Spline 1-knot hazard	✓	✓	↑	✗	✗
Spline 2 knots hazard	✓	✓	↑	✗	✓
Spline 1-knot odds	✓	✓	↑	✓	✗
Spline 2 knots odds	✓	✓	↑	✓	✗
Spline 1-knot normal	✓	✓	↑	✓	✓

the spline model analysis, for example whether default spline knots were used.

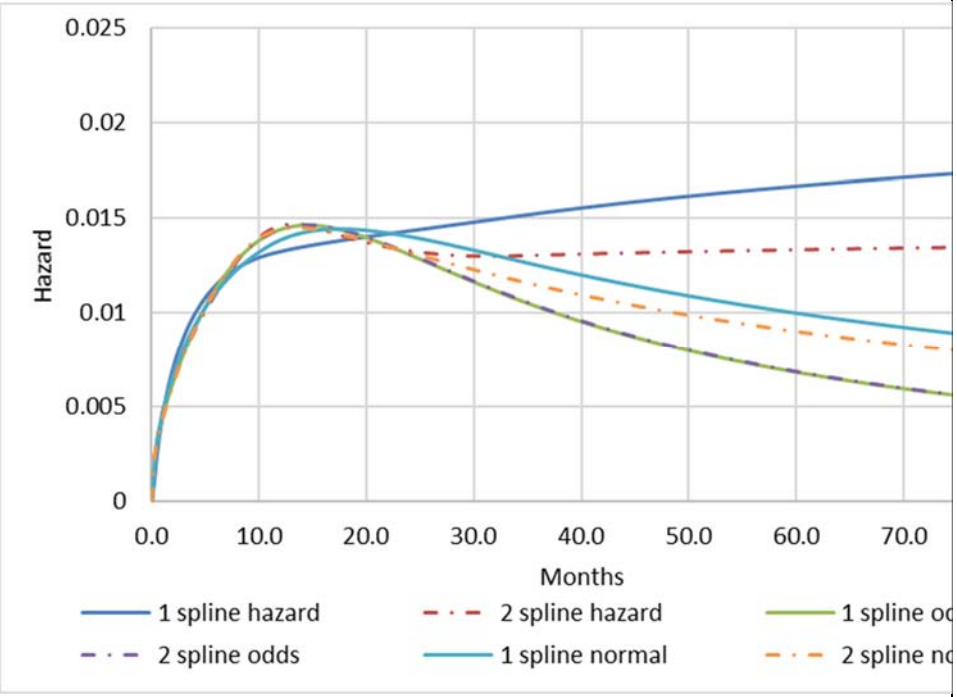
The company noted the improved within-trial fit of the spline models. The ERG considers that within-trial fit should not be viewed in isolation because of data immaturity, and given that the large majority of the life-years gained in the model are accumulated beyond the observed period. It is stated in TSD 21 that spline models generally provide good within-trial-fits – however, they do not necessarily improve extrapolation. Extrapolation is completely based on the linearity assumption (on a transformed scale of the survival function), which may result in implausible projections. Especially with data immaturity being an issue in this appraisal, it is concerning that spline models cause the extrapolation to be based upon the trends towards the end of follow-up, which in this case may be based on a small number of events.

The company also considered this model to fulfil the criteria of providing the appropriate hazard

Spline 2 knots normal	✓	✓	↑	✓	✓	

As can be seen from the table, all spline models provide a reasonable fit to the within-trial data. However, as presented in the table and in Figure 1 the spline hazard models did not have a hazard function with an initial increase and decreases over time in line with the MAPS data.

Figure 1. PDC Independent Spline Hazard Function



As presented in the response to clarification questions and the company

function (first increasing and then decreasing) and providing plausible survival predictions as stated by clinical experts.

The company did not provide any detail on spline models applied to the nivolumab + ipilimumab arm, however, these are implemented in the model. The ERG tested the use of a spline 2 knots normal model for use in the nivolumab + ipilimumab arm conditional on the company's base-case, which increased the ICER significantly (from company base-case £77,669 to £173,191 per QALY gained). This illustrates that the extrapolation using spline models can be extremely volatile, and underlines the uncertainty about OS given the immature data.

For the above-mentioned reasons (log-logistic fulfilled all criteria if MAPS is used for external validation of clinical plausibility, spline models do not necessarily improve extrapolation and may result in biased extrapolations when the number of events near the last knot is low, and not much detail provided on the spline model

		submission the clinical experts consulted during the development of the company submission considered that rates of 5-year, 7.5-year and 10-year survival for PDC patients would be 5%, 2% and 0%, respectively. With regards to predicted survival, spline 1-knot hazard and spline 1 and 2 knots odds were therefore considered not to be appropriate (resulting in 3%, 6% and 6% survival at 5 years, respectively, and with patients surviving until 15 years with spline 1 and 2 knots odds). However, spline 2 knots hazard and spline 1 and 2 knots normal resulted in clinically plausible long-term survival. Of these, spline 2 knots normal might be seen to be on the high end, and 2-knots hazards on the lower end for 5- and 10-year survival. To inform the selection of the most clinically plausible survival extrapolation, the spline models fitted were validated with a UK clinical expert. Landmark survival estimates from these models were presented together with predicted survival from the log-logistic distribution preferred by the ERG. The clinical expert stated that the survival predictions from the log-logistic distribution would be too optimistic and that survival would be < 2% at Year 10. This is also aligned with prior clinical input received where 10-year survival for PDC was thought to be 0%. Of the distributions fitted to the PDC data, the clinical expert selected the spline 2-knots normal as the most appropriate but stated that some of the other spline models predicting similar low long-term survival are also plausible. Based on the overall assessment presented in Table 2 as well as the clinical validation, Spline 2-knots normal has therefore been selected as the new base case extrapolation for the PDC arm. It is also clear from the clinical validation that the log-logistic distribution selected for PDC by the ERG results in clinically implausible long-term survival predictions.	analysis), the ERG maintains its base-case. However, the ERG also considers the company's spline models as valid scenarios as ultimately it has to be acknowledged that the long-term OS in the nivolumab + ipilimumab arm is uncertain. In addition, scenarios using spline models for the nivolumab + ipilimumab arm could be informative, too.

Table 2. Absolute OS Analysis for Independent Models Fitted to Pemetrexed + Cisplatin or Carboplatin

		Absolute Survival (%)								
Data Set	Curve	6 mos	Year 1	Year 2	Year 3	Year 5	Year 10	Year 15	Year 20	Median (mos)
CheckMate 743	Kaplan-Meier	82.2	57.7	27.0	15.2	-	-	-	-	14.10
Zalcman 2016 (MAPS) pemetrexed + cisplatin	Kaplan-Meier	88.8	63.4	33.6	15.7	8.1	-	-	-	16.1
Pemetrexed + cisplatin / carboplatin extrapolation	Log-logistic	81.7	57.3	28.6	16.5	7.5	2.4	1.2	0.7	13.80
	Spline 1-knot hazard	81.1	58.5	28.1	13.0	2.5	0.0	0.0	0.0	14.72
	Spline 2-knots hazard	82.1	58.2	27.7	14.1	3.6	0.1	0.0	0.0	14.49
	Spline 1-knot odds	82.0	58.1	27.5	15.1	6.3	1.8	0.8	0.5	14.49
	Spline 2-knots odds	82.1	58.1	27.5	15.0	6.3	1.8	0.8	0.5	14.49

With regards to treatment waning, the ERG acknowledged that the time point of 5 years was arbitrary and chosen to be in line with previous committee preferences for other topics. However, it also has to be re-iterated that there is a lack of evidence for a lasting treatment effect and the company's arguments are based on opinion of one expert without long-term experience with nivolumab + ipilimumab in MPM. There is therefore substantial remaining uncertainty about long-term OS for patients treated with nivolumab + ipilimumab and the ERG disagrees that its assumption lacks clinical plausibility but acknowledges that the true long-term treatment effect is currently unknown.

The ERG acknowledges that different scenarios should be considered, that the company's base-case assumption of no additional treatment waning may be a valid scenario and that further expert opinion may add limited information given that there is

Spline 1-knot normal	81.8	58.7	27.6	13.9	4.4	0.5	0.1	0.0	14.72
Spline 2-knots normal	82.1	58.0	27.6	14.6	5.1	0.8	0.2	0.0	14.49

Modelling of long-term treatment effect

As presented in the company submission and reiterated in the company response to clarification questions, there is long-term evidence of a robust and durable treatment effect lasting beyond discontinuation for immunotherapies. This robust and durable treatment effect lasting beyond discontinuation for immunotherapies has been shown in several indications for immunotherapies (NICE TA357, NICE TA366, NICE TA384, NICE TA400, NICE TA553, NICE TA558). Further, it is important to bear in mind that any modelling of changes of treatment effect with time directly effects the long-term survival extrapolations.

As presented in the company submission, the company response to clarification questions and in this document, selection of the most appropriate survival curves to be used in the model has been guided by clinical input on the plausibility of long-term survival. Based on this input the log-logistic distribution was perceived as providing the most clinically plausible long-term predictions for nivolumab + ipilimumab and Spline 2-knots normal for PDC. As can be seen from Table 3, the incorporation of treatment waning as proposed by the ERG would result in a significant reduction in the proportion of patients estimated to be alive at 10 years. Therefore, predicted OS for nivolumab + ipilimumab would no longer be clinically plausible as advised by the clinical experts in preparation of the company submission. This highlights that the

currently no long-term clinical experience with nivolumab + ipilimumab in MPM (only three patients were at risk at 36 months according to Table 13 in the clarification letter). Moreover, it is unclear to the ERG how the expert opinion was exactly derived (how was the expert selected, why specifically this expert and what questions were asked and how). Furthermore, if expert opinion is sought, or indeed for presentation at committee, the ERG considers it informative to present the (tabulated) OS curves with different treatment waning assumptions and OS modelling choices, rather than the hazard ratio curves.

The company's did not provide compelling arguments for the ERG to adjust the treatment waning assumption in its base-case. As stated in the ERG report, there is precedence to use the five-year treatment waning time point (as done by the ERG) but the ERG acknowledges that the selected time point is arbitrary.

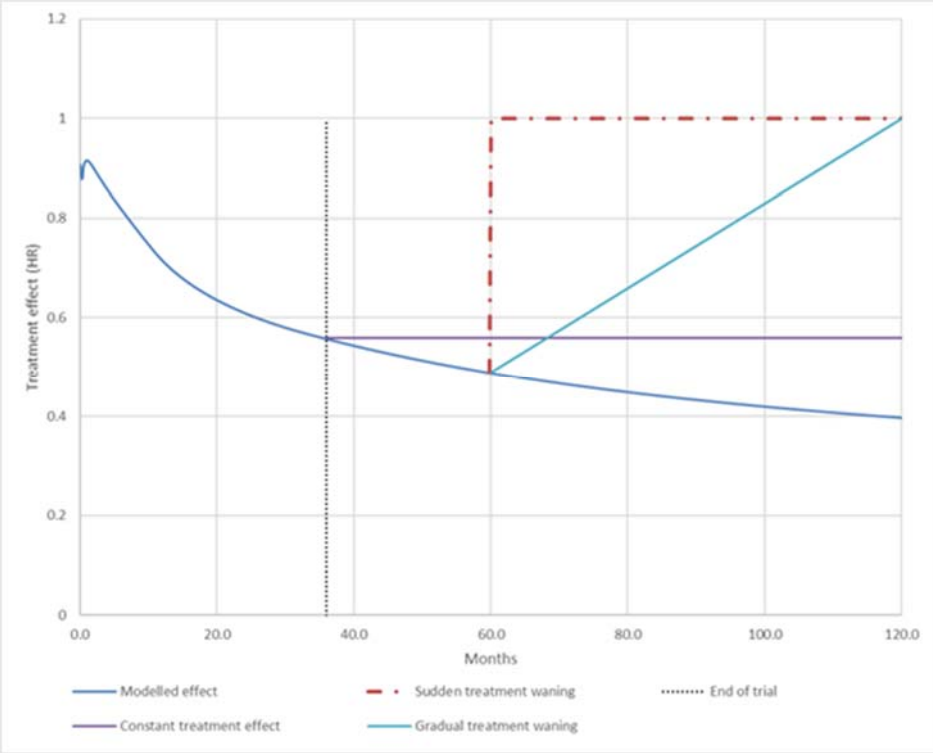
treatment effect and extrapolations cannot be considered in isolation; the overall clinical plausibility of the extrapolations needs to be the primary basis for validation, considering both the distributions for extrapolation and any waning of treatment effect.

Table 3. Absolute OS Estimates for Nivolumab + Ipilimumab With Different Treatment Effect Waning Scenarios

	Absolute Survival (%)					
Scenario	**6 mos**	**Year 1**	**Year 2**	**Year 3**	**Year 5**	**Year 10**
Modelled without treatment waning	84.0%	65.2%	40.1%	26.8%	14.6%	5.7%
ERG proposed sudden treatment waning from Year 5	84.0%	65.2%	40.1%	26.8%	14.6%	2.2%
Constant treatment effect from Year 5	84.0%	65.2%	40.1%	26.8%	14.6%	5.2%

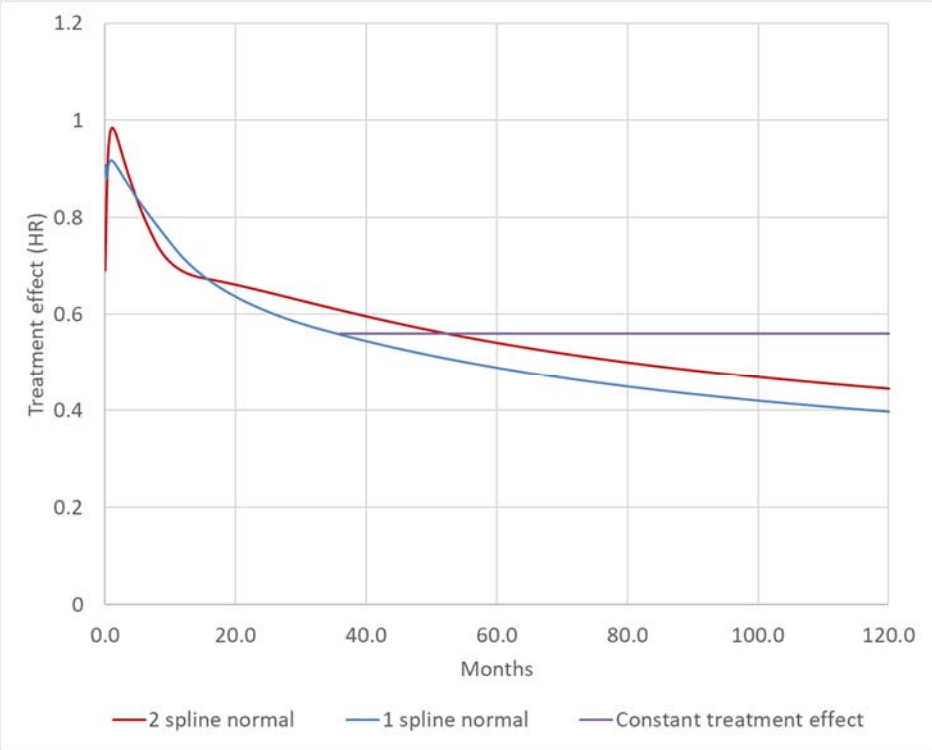
		To further inform the modelling of long-term treatment effect clinical expert advice was sought in preparation of this response. The clinical expert was presented with alternative scenarios of treatment effect over time (Figure 2) to assess what is most clinically plausible. The clinical expert reiterated what was presented in the company submission that he would anticipate a durable treatment effect with a dual immunotherapy treatment, as has been observed in other indications, with a proportion of patients having a long-term durable response. Whereas all benefits from PDC were predicted to be lost by Year 5. Of the presented assumptions of treatment effect over time the clinical expert thought that the ERG proposed sudden loss of treatment effect was unthinkable and lacked clinical validity. He thought that the presented modelled treatment effect (based on log-logistic for nivolumab + ipilimumab and spline 1-knot normal for PDC) seemed a bit optimistic and that the continued constant treatment effect would be the worst-case scenario. Thus, he stated that the most likely treatment effect over time would be somewhere in between the two scenarios. Based on this clinical input we argue that the suggested waning by the ERG lacks clinical plausibility. Further, as noted earlier we argue that waning of treatment effect cannot be viewed in isolation from the selected survival extrapolation. Figure 3 presents the resulting treatment effect from the economic model with the distributions deemed to be the most clinically plausible (updated company base case) together with the scenario presented to the clinical expert. As can be seen from the figure the updated base case (log-logistic for nivolumab + ipilimumab and spline 2-knot normal for PDC) in fact result in a long-term treatment effect in more in line with what the clinical expert thought would be the most clinically plausible long-term treatment effect.	

Figure 2. Plot of Hazard Ratio Over Time Under Different Waning of Treatment Effect Assumptions



Note: Modelled effect is based on log-logistic for nivolumab + ipilimumab and spline 1-knot normal for PDC.

Figure 3. Plot of Hazard Ratio Over Time With 1 and 2-Knots Spline Normal Selected for PDC Extrapolation



Therefore, based on the clinical input provided, the log-logistic distribution without waning results in the most appropriate distribution to

<table>
<tr><td></td><td></td><td>use for nivolumab + ipilimumab (to which the ERG agreed) and thus should be seen to adequately capture the long-term survival without treatment waning being applied. However, as a conservative scenario analysis the assumption of constant treatment effect from Year 5 has been investigated resulting in increased revised base case ICER from £77,669 to £81,043. As can be seen from Table 3 the this provides a more conservative 10-year survival estimate compared to no treatment waning but still within a range that could be clinically plausible contrary to the ERGs waning assumption.</td><td></td></tr>
<tr><td>Key issue 10: Health-related quality of life – duration of utility benefits for nivolumab + ipilimumab</td><td>YES</td><td>Patient-reported outcomes measured in CM743 included the Lung Cancer Symptom Scale-Mesothelioma and EQ-5D-3L. Analyses of CM743 have showed that improvements in health-related quality of life for patients who received nivolumab + ipilimumab were maintained when compared with PDC (Scherpereel et al., 2020; Popat et al., 2021). In addition, symptom burden scores improved for patients who received nivolumab + ipilimumab compared with baseline versus a trend to deterioration for patients who received PDC. However, it is unclear whether these benefits will continue beyond the trial follow-up period.

We have explored additional scenarios of using treatment-dependent utilities until alternative time points other than 3 years. The resulting ICERs are presented below in Error! Reference source not found..

Table 4. Scenario analysis results exploring duration of treatment-dependent utilities
<table>
<tr><th>Scenario</th><th>ICER (£/QALY)</th></tr>
<tr><td>Treatment-dependent utilities until 3 years</td><td>£77,669</td></tr>
<tr><td>Treatment-dependent utilities until 5 years</td><td>£76,304</td></tr>
<tr><td>Treatment-dependent utilities until 7.5 years</td><td>£75,609</td></tr>
</table></td><td>The ERG notes the company’s scenarios illustrating the magnitude of impact of alternative assumptions regarding the duration of treatment benefit on quality of life, conditional on the company’s original base-case, and considers them potentially informative.</td></tr>
</table>

		Treatment-dependent utilities until 10 years £75,290 Treatment-dependent utilities over 20-year time horizon £74,897	
Key issue 11: Resources and costs – estimation of time to treatment discontinuation	**YES**	As presented in the company submission, and the response to clarification questions, we maintain that the mean doses would be the best data source for estimation of treatment costs as it adequately reflects both treatment duration as well as dose intensity. The clinical expert consulted in preparation of this response also confirmed that he thought this would be representative of use in clinical practice. Further, as presented in the company submission, the fit of standard parametric models to the trial data was poor. However, to meet the ERG's request for parametric models to be included in the model further analyses has been undertaken so that a scenario can be presented with parametric distributions. To improve the fit of the parametric distributions for the nivolumab + ipilimumab arm survival analyses has been conducted per time to treatment discontinuation per nivolumab and ipilimumab treatment. In addition, spline models have been fitted to both the nivolumab, ipilimumab and PDC data to investigate if this would offer improved fit to the trial data. The full outcome of the survival analysis can be found in Appendix A. Based on the updated survival analysis splitting the analyses with nivolumab and ipilimumab specific survival analyses offer better fit to the data. For nivolumab of the standard distribution generalised gamma provide relatively good fit to the data. However, 1-knot spline hazard provides better visual fit and similar statistical fit and was therefore seen as a more appropriate distribution to use.	The ERG welcomes this analysis and notes that the impact on the ICER is indeed small. The ERG adopts this in their base-case, given that there are concerns about potential under-estimation of costs using the mean number of doses approach.

		For ipilimumab none of the standard distributions provide good visual fit to the data. Of the spline models both odds and hazard models provided reasonable visual and statistical fit while spline normal models did not converge. Of the spline hazard and odds models the 2-knots spline hazard model was deemed to provide the best fit to the data and therefore used in the analysis. For PDC visual fit of the spline models was relatively poor except for 3-knots spline odds and hazard models. Specifically, 3-knots spline models is needed to adequately capture the later part of the time to treatment discontinuation data for PDC (month 3-4) as both 1 and 2-knots models have a poor fit to the data. Thus, to allow for a scenario where the PDC arm time to treatment discontinuation is modelled with a parametric model the 3-knots hazards model was selected based on best visual and statistical fit to the data. In the scenario with parametric models fitted it should be noted that dose intensity has not been applied and thus would be likely to overestimate the number of doses received compared with clinical practice. Basing the time to treatment discontinuation on the parametric models instead of mean number of doses increased the revised base case ICER from £77,669 to £78,803.	
Key issue 12: resources and costs - uncertainty about subsequent treatments	**NO**	Per our response to Key Issue 4, there are currently no second-line therapies licensed for use in MPM. However, nivolumab monotherapy is being used in the NHSE in England under interim treatment options during the COVID-19 pandemic (NICE, 2021); 388 patients were treated with nivolumab monotherapy in this indication from August 2020 to April 2021. During technical engagement, the use of subsequent therapies was again validated with a UK clinician who noted that under the current guidance nivolumab monotherapy is the only approved treatment for	The ERG appreciates the additional scenarios performed by the company. These confirm that the impact of changes to subsequent treatment duration is small. However, it remains difficult in the re-submitted model to select differential subsequent treatment duration per initial treatment without

		patients who progress from PDC and, if reimbursed, patients receiving nivolumab + ipilimumab who progress would receive PDC. If nivolumab monotherapy is not available, vinorelbine is expected to be the next line of treatment following PDC. The clinician estimated that the average duration of second-line nivolumab monotherapy is 2 to 3 months, which aligns with the median duration of 84 days from the CONFIRM trial. The clinician estimated that the duration of second-line PDC following nivolumab + ipilimumab is 2.5 months, and vinorelbine following PDC is 2 months. We have performed a scenario analysis in which all patients who receive subsequent treatment after progressing from PDC get nivolumab monotherapy for a duration of 84 days and all patients who receive subsequent treatment after progressing from nivolumab + ipilimumab get PDC (66% carboplatin and 34% cisplatin) for a duration of 2.5 months. This scenario decreases the revised base case ICER from £77,669 to £75,552. An additional scenario without nivolumab monotherapy has been explored. All patients who receive subsequent treatment after progressing from PDC get vinorelbine for a duration of 1.7 months (aligning with the model base case) and all patients who receive subsequent treatment after progressing from nivolumab + ipilimumab get PDC (66% carboplatin and 34% cisplatin) for a duration of 2.5 months. This scenario increases the revised base case ICER from £77,669 to £81,522. However, as noted in response to Key Issue 4, initial assessment of adjusting for subsequent immunotherapy following PDC indicates that in this scenario the treatment effect for nivolumab + ipilimumab will improve and thus the ICER will decrease.	altering the distribution of subsequent treatments per initial treatment. The ERG therefore considers that with the availability of future data, this issue should still be explored.
Key issue 13: Resources	**NO**	Due to the very low incidence of these events and small differences between treatment arms, the impact to the ICER will be minor. The	The ERG is satisfied that this is indeed a minor issue.

and costs – adverse events

difference in adverse event costs in the base case analysis accounts for approximately 1% of the total incremental costs. Utility decrements for adverse events are not applied in the base case analysis that uses treatment-dependent utilities (to avoid double-counting).

We have run a scenario to estimate the impact on the ICER using a 1% cut-off for the inclusion of grade 3+ adverse events. We identified all additional adverse events that would be included with a 1% cut-off from CM-743 supplementary table S.6.4.2. The incidence of each adverse event for nivolumab + ipilimumab and PDC is presented below in Table 5.

Table 5. Incidence of additional grade 3+ drug-related adverse events for nivolumab + ipilimumab and PDC with a 1% cut-off from CM-743

Grade 3+ AE	Nivolumab + Ipilimumab Incidence	PDC Incidence
Pruritus	1.0%	0.0%
Rash	1.3%	0.0%
Fatigue	1.0%	1.8%
Alanine aminotransferase increased	1.7%	0.7%
Aspartate aminotransferase increased	1.0%	0.4%
Hypopituitarism	1.0%	0.0%
Infusion related reaction	1.0%	0.7%
Pneumonitis	1.0%	0.0%

		Hepatic function abnormal: 1.7% / 0.7% Immune-mediated hepatitis: 1.0% / 0.0% Drug-induced liver injury: 1.0% / 0.4% Hepatitis: 1.0% / 0.0% Febrile neutropenia: 0.0% / 1.1% Pancytopenia: 0.0% / 1.8% Acute kidney injury: 1.3% / 0.0% Total: 15.0% / 7.6% The difference in total incidence of 7.4% and mean adverse event cost of £1,277.76 (calculated from the existing adverse event costs in the model) was applied to calculate an additional cost of £94.55 for nivolumab + ipilimumab. This increased the revised base case ICER from £77,669 to £77,810.	
Key issue 14: Company's cost effectiveness results – proportion of progression-free life years (PF LYs) accumulated beyond the	**NO**	A partitioned survival model approach was used with PF LYs generated directly from the PFS curves for nivolumab + ipilimumab and PDC (calculated using the area under the curves). Justification for the selection of PFS survival models and validation of the long-term extrapolations has been provided in response to clarification questions. A large proportion of the PF LYs are gained beyond the observed data period for nivolumab + ipilimumab compared with PDC. This occurs because PFS for PDC is initially higher than PFS for nivolumab + ipilimumab (a pattern of initially poor PFS followed by longer-term PFS benefits for patients who respond well to immunotherapy has been seen across different indications). In the company base case analysis PFS is	The company's response is helpful. Uncertainty remains about the magnitude of post-trial period PFS.

observed data		higher for PDC until the curves cross in model cycle number 42 (9.7 months), from which point PFS remains higher for nivolumab + ipilimumab. Consequently, cumulative PF LYs are higher for PDC until model cycle 92 (21.2 months). Therefore, incremental PF LYs are positive for nivolumab + ipilimumab from 21.2 months and most of the total benefit is generated beyond the observed data period.	

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key Issue(s) in the ERG Report that the Change Relates to	Company's Base Case Before Technical Engagement	Change(s) Made in Response to Technical Engagement	Impact on the Company's Base-Case ICER
Original Base case			**77,531**
[redacted]	[redacted]	[redacted]	[redacted]
Key issue 9: Treatment effectiveness and extrapolation – immaturity of the long-term progression-free survival (PFS) and overall survival (OS) data	Extrapolation of PDC survival Original company preferred OS extrapolation was hybrid log-logistic for nivolumab + ipilimumab and hybrid exponential for PDC	Following the ERG response and further clinical input on survival extrapolations log-logistic without hybrid modelling has been selected for the nivolumab + ipilimumab arm and spline 2-knots normal for the PDC arm	74,897 [redacted]
Key issue 10: Health-related quality of life – duration of utility benefits for nivolumab + ipilimumab	Treatment-dependent utility values were applied for the full duration of the analysis	Following the ERG response treatment independent utility values have been applied from Year 3 and onward	76,732 [redacted]
Company's preferred base case following technical engagement		Based on the response provided above the following changes have been incorporated into the company's base case: • [redacted] • 2 knots spline normal distribution for extrapolation of PDC OS • Treatment independent utility values applied from Year 3	77,669 [redacted]

References

Baas P, Daumont MJ, Lacoin L, Penrod J, Carroll R, Tanna N. Treatment patterns and outcomes in malignant pleural mesothelioma in England: a nationwide CAS registry analysis from the I-O Optimise initiative [poster 1909P]. Presented at the European Society for Medical Oncology Virtual Congress; 19-21 September 2020.

Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet. 2021 Jan 30;397(10272):375-86.

Bristol Myers Squibb (BMS). Efficacy and safety data to support flat dosing of nivolumab in mesothelioma subjects. BMS936558. 14 August 2020.

EMA. OPDIVO SmPC. OPDIVO (nivolumab) summary of product characteristics. Bristol Myers Squibb; 2020. Available at: Opdivo, INN-nivolumab (europa.eu). Accessed 14 May 2021.

Fennel D, Ottensmeier C, Califano R, Hanna GG, Weings S, Hill K, et al. Nivolumab versus placebo in relapsed malignant mesothelioma: Preliminary results from the CONFIRM Phase 3 Trial. Presented at the 2020 World Conference on Lung Cancer Singapore. January 28-31, 2021. Worldwide Virtual Event.

NICE. Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy. TA490. 22 November 2017. Available at: https://www.nice.org.uk/guidance/ta490/history. Accessed 14 May 2021.

NICE. NHS England interim treatment options during the COVID-19 pandemic. NG161. Available at: https://www.nice.org.uk/guidance/ng161/resources/interim-treatment-change-options-during-the-covid19-pandemic-endorsed-by-nhs-england-pdf-8715724381. Accessed 14 May 2021.

NICE. Nivolumab for treating advanced (unresectable or metastatic) melanoma. TA384. 18 February 2016. Available at: https://www.nice.org.uk/guidance/ta384. Accessed 14 May 2021.

NICE. Nivolumab in combination with ipilimumab for treating advanced melanoma. TA400. 27 July 2016. Available at: https://www.nice.org.uk/guidance/ta400. Accessed 14 May 2021.

NICE. Pembrolizumab for advanced melanoma not previously treated with ipilimumab. TA366. 25 November 2015. Available at: https://www.nice.org.uk/guidance/ta366. Accessed 14 May 2021.

NICE. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab. TA357. 07 October 2015. Available at: https://www.nice.org.uk/guidance/ta357. Accessed 14 May 2021.

NICE. Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease. TA558. 23 January 2019. Available at: https://www.nice.org.uk/guidance/ta558. Accessed 14 May 2021.

NICE. Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence. TA553. 19 December 2018. Available at: https://www.nice.org.uk/guidance/ta553 Accessed 14 May 2021.

Popat S, Scherpereel A, Antonia S, Oulkhouir Y, Bautista Y, Cornelissen R, Greillier L, et al. First-Line Nivolumab Plus Ipilimumab Versus Chemotherapy in Unresectable Malignant Pleural Mesothelioma (MPM) in CheckMate 743. iMig MS02:08 7 May 2021. Available at: https://imig2021.org/wp-content/uploads/2021/05/imig2021_Virtual_programmebook.pdf.

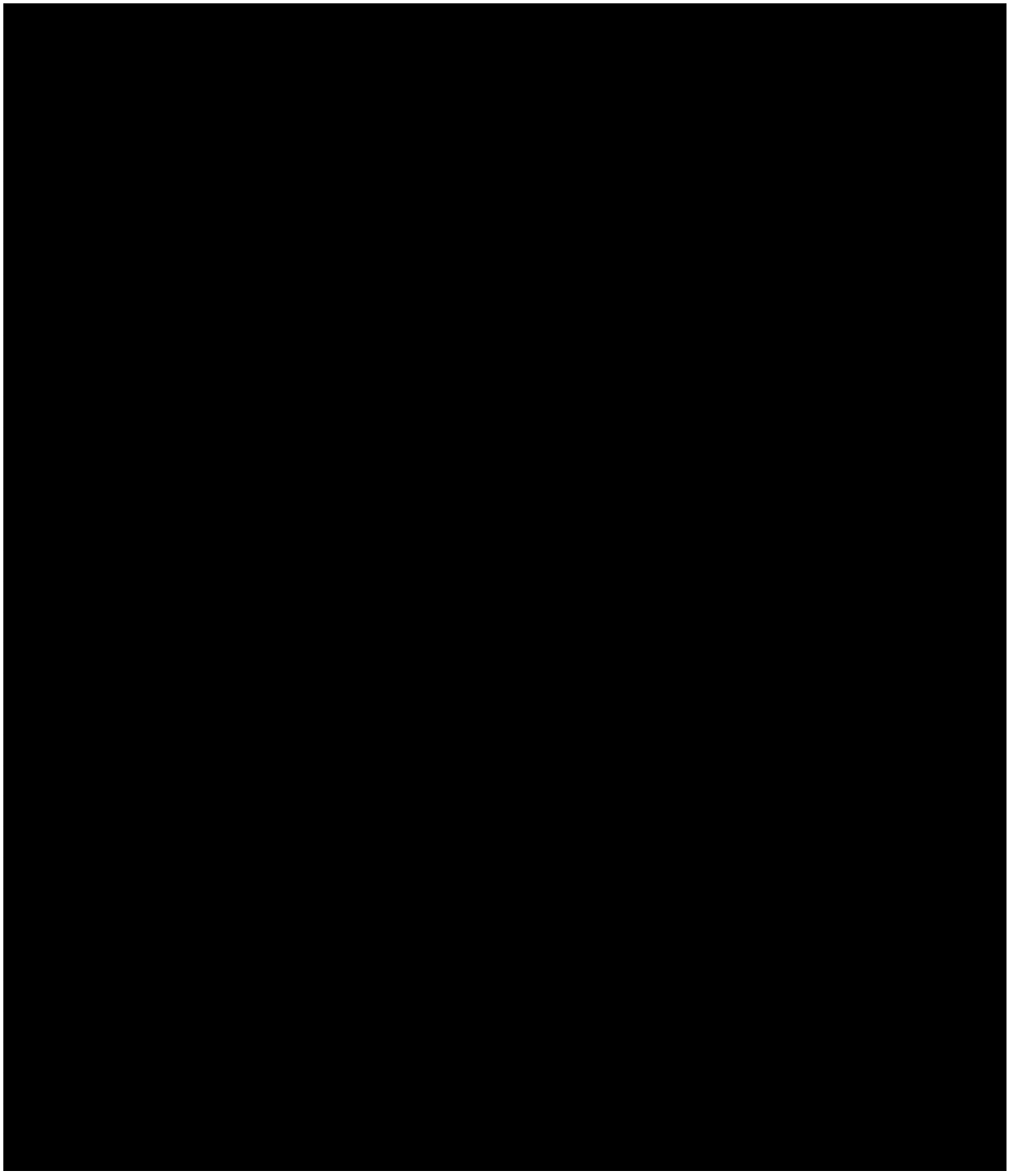
Scherpereel A, Antonia S, Bautista Y, Grossi F, Kowalski D, Zalcman G et al. First-line nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) for the treatment of unresectable malignant pleural mesothelioma (MPM): Patient-reported outcomes (PROs) from CheckMate 743. ESMO LBA1 1 December 2020. Available at: https://www.annalsofoncology.org/article/S0923-7534(20)43159-X/fulltext

Appendix A

Updated survival analyses of CheckMate-743 time to treatment discontinuation data

[redacted]

[redacted]

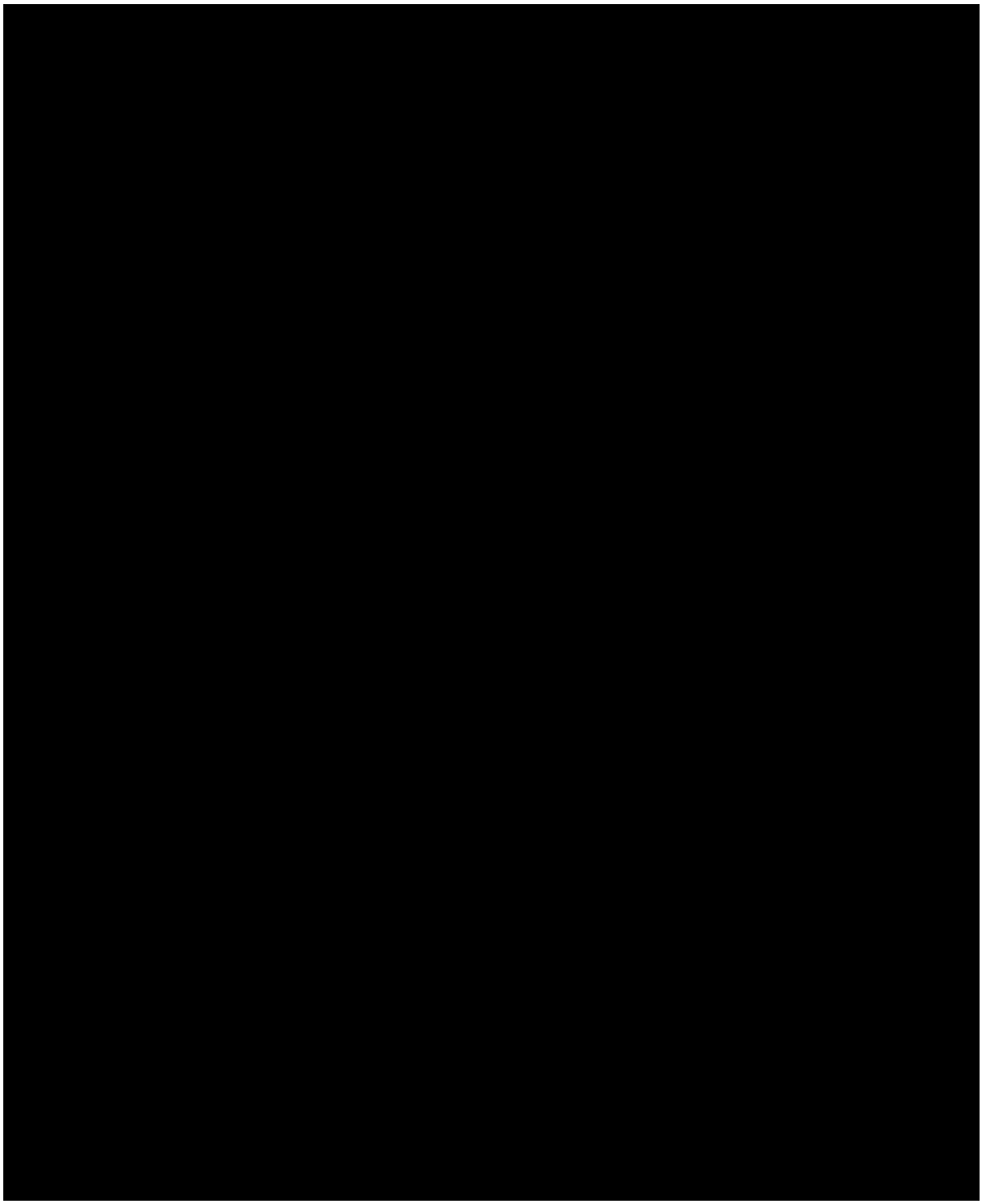


[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

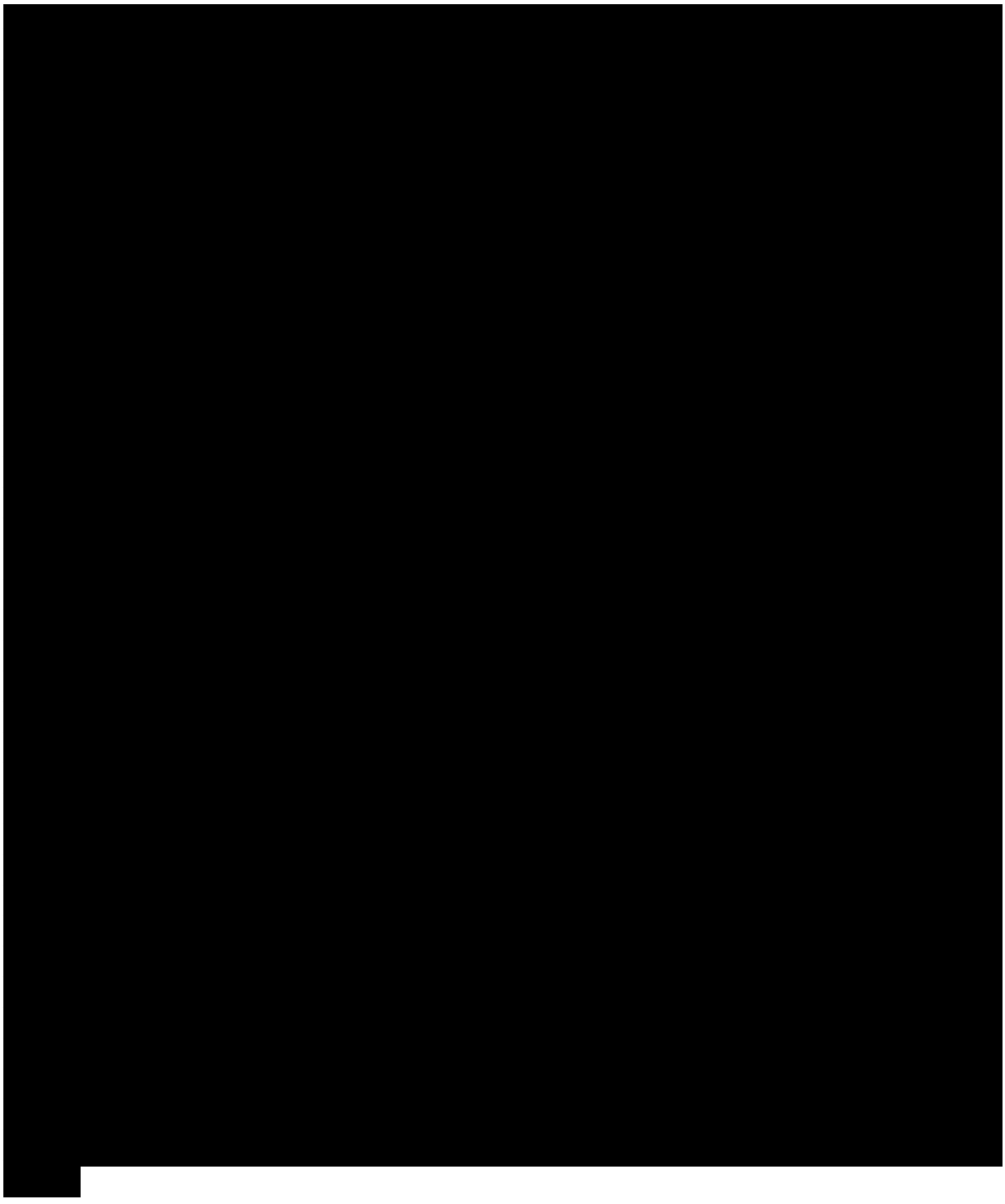
[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]



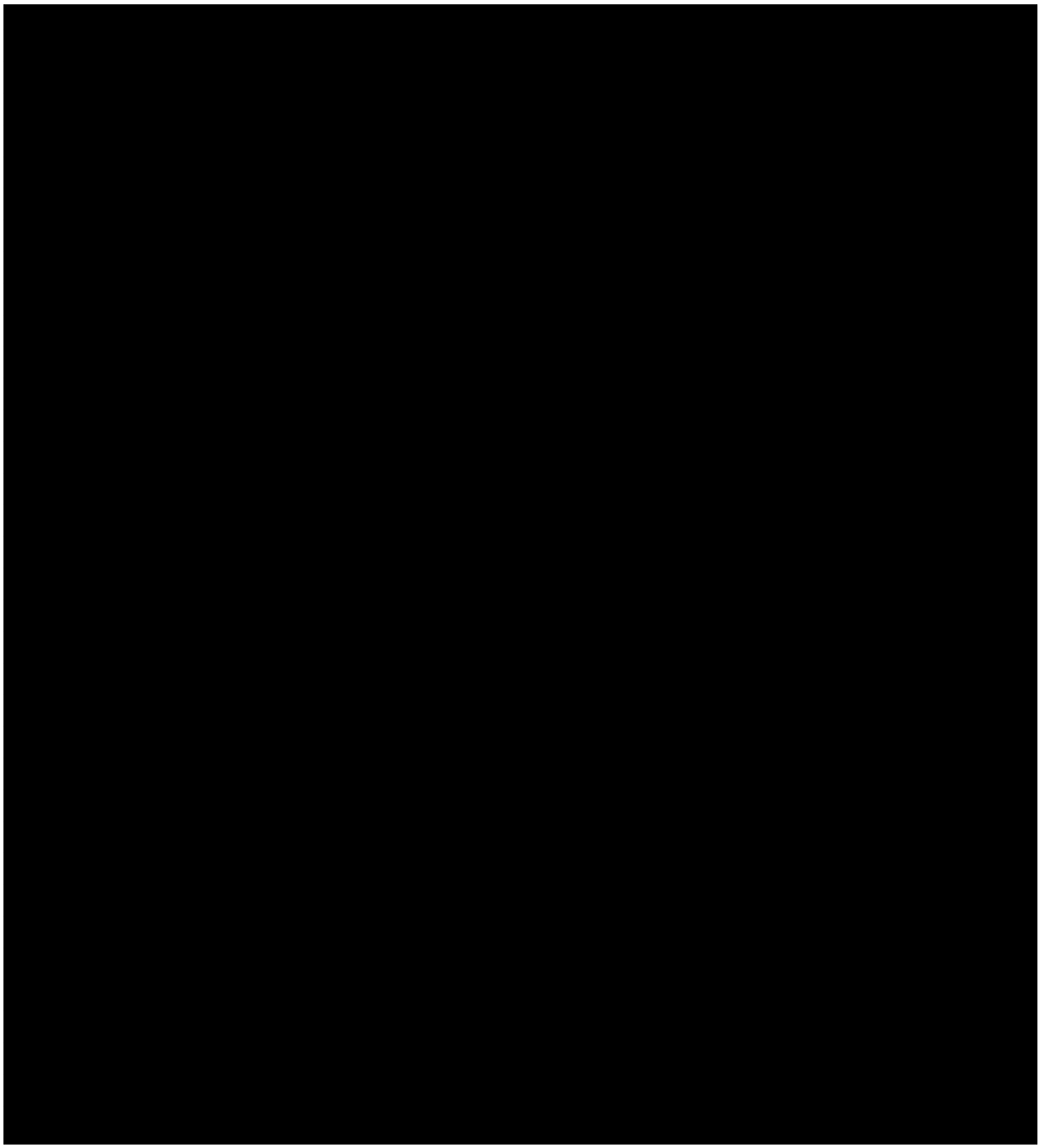
[redacted]

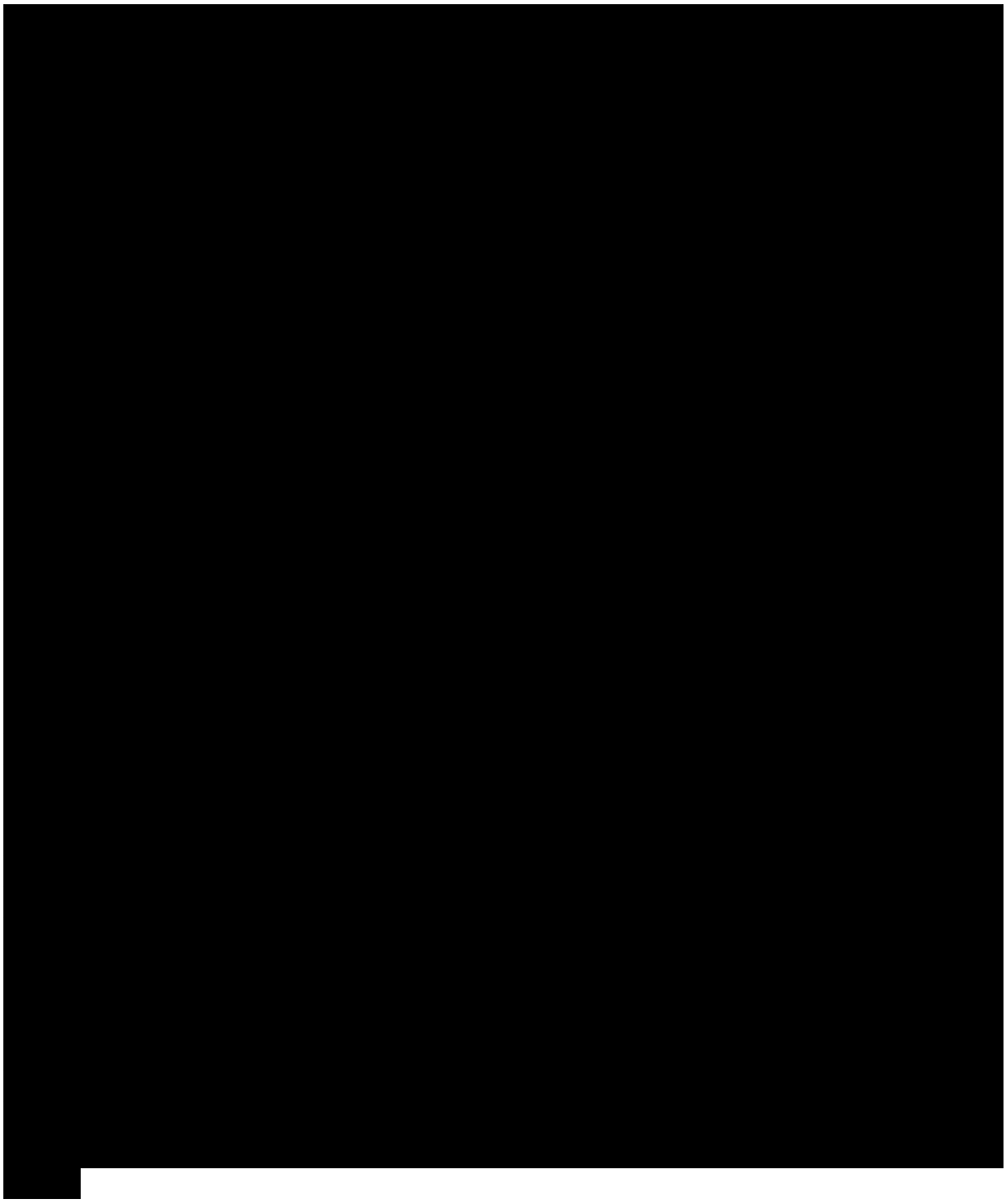
[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]





[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

ADDENDUM: Response to Technical Engagement

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Authors
Nigel Armstrong, Health Economist, KSR Ltd
Sabine Grimm, Health Economist, Maastricht UMC, the Netherlands
Bram Ramaekers, Health Economist, Maastricht UMC, the Netherlands
Marie Westwood, Reviews Manager, KSR Ltd
Annette Chalker, Systematic Reviewer, KSR Ltd
Mohammed Islam, Health Economist, KSR Ltd
Gill Worthy, Statistician, KSR Ltd
Shelley De Kock, Information Specialist, KSR Ltd
Manuela Joore, Health Economist, Maastricht UMC
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to Nigel Armstrong, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, United Kingdom
YO19 6FD

Date completed 31/05/2021

ERG model changes based on the company's response to technical engagement

The company provided a new model in which further analyses and [redacted] were implemented. The ERG used this model to implement its new base-case and scenario analyses, as shown in Tables 1 and 2.

The following changes were made to the company's model (please see the response to the company's technical engagement submission for justification), all of which were matters of judgement (Table 1):

- Use the log-logistic distribution for the comparator arm OS
- Implement treatment waning from 5 years onwards
- Use company's parametric distributions (spline models) to model TTD

The ERG conducted the following scenario analyses conditional on the ERG base-case (Table 2):

1. a) PFS: use the log-logistic distribution for both arms
   b) PFS: use the generalised gamma distribution for both arms
2. Use the company's spline-based OS model for the PDC arm (with treatment waning)
3. Use the company's spline-based OS model for both treatment arms (with treatment waning)
4. Treatment waning only at 10 years

Table 1: Revised ERG base-case, based on company's updated technical engagement model (deterministic unless indicated)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company's revised base-case after TE							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	52,010	0.903	0.670	77,669
Matter of judgement 2: use log-logistic distributions for OS in both treatment arms (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	50,966	0.710	0.550	92,669
Matter of judgement 3: implement treatment waning from 5 years onwards (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,007	0.621	0.478	106,675
Matter of judgement 5: use parametric distributions for TTD (key issue 11)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	52,769	0.903	0.670	78,803
ERG base-case (Changes 2, 3, 5)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,729	0.617	0.476	108,650

ERG base-case probabilistic (5,000 runs)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,703	0.615	0.476	108,599

Table 2: Revised ERG scenarios conditional on revised ERG base-case (deterministic)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ERG base-case							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,729	0.617	0.476	108,650
Scenario 1a: PFS log-logistic distribution for both arms (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	52,263	0.617	0.460	113,703
Scenario 1b: PFS generalised gamma distribution for both arms (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	52,004	0.617	0.467	111,365
Scenario 2: Company's spline-based OS model for PDC arm (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,767	0.621	0.478	108,263
Scenario 3: Spline-based OS model for nivolumab + ipilimumab (2 knots normal) and PDC arms (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	50,196	0.333	0.299	167,762

Scenario 4: Treatment waning at 10 years (key issue 9)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,808	0.617	0.476	113,015