

6.07 NIVOLUMAB PLUS IPILIMUMAB,

Nivolumab,

Injection concentrate for I.V. infusion 40 mg in 4 mL,

Injection concentrate for I.V. infusion 100 mg in 10 mL,

Opdivo[®],

Ipilimumab,

Injection concentrate for I.V. infusion 50 mg in 10 mL,

Yervoy[®],

Bristol-Myers Squibb Australia Pty Ltd

1 Purpose of submission

- 1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy) listing for nivolumab plus ipilimumab (herein referred to as NIVO+IPI) for the treatment of unresectable malignant pleural mesothelioma (MPM). NIVO+IPI is currently PBS listed for malignant melanoma and renal cell carcinoma (RCC). This was the first PBAC consideration of NIVO+IPI for MPM.
- 1.2 Listing was requested on the basis of a cost-utility analysis versus pemetrexed plus cisplatin or pemetrexed plus carboplatin (herein referred to as pemetrexed-based chemotherapy) in the first-line setting (Table 1). The submission did not provide an economic evaluation for the use of NIVO+IPI in the second- or later-line setting. The ESC considered the economic evaluation presented (in the first-line setting) was not generalisable to the second- or later-line setting, and the ICER was likely to be higher in that setting.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with unresectable malignant pleural mesothelioma
Intervention	Nivolumab plus ipilimumab
Comparator	Main comparator: pemetrexed-based chemotherapy in the first-line setting. Supplementary comparator: best supportive care (including pemetrexed rechallenge) in the second-line setting
Outcomes	Overall survival, progression-free survival, objective response rate, duration of response, health-related quality of life, rate and nature of adverse events.
Clinical claim	Superior in terms of efficacy with a different and non-inferior safety profile compared with pemetrexed-based chemotherapy. Superior in terms of efficacy with a different and non-inferior safety profile compared with best supportive care.

Source: Table 1, p17 of the submission.

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** not registered.

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2.2 The submission was made under the parallel TGA/PBAC process for the first-line setting. No TGA registration was sought for use in the second- or later-line setting. The submission stated that a priority review designation has been granted for the TGA assessment of NIVO+IPI. The TGA Delegate’s Overview was received prior to the PBAC meeting and the Delegate was supportive of registering nivolumab and ipilimumab for the following indications:

“(Nivolumab), in combination with ipilimumab, is indicated for the first-line treatment of patients with unresectable malignant pleural mesothelioma.

(Ipilimumab), in combination with nivolumab, is indicated for the first-line treatment of patients with unresectable malignant pleural mesothelioma.”

2.3 NIVO+IPI was assessed under “Project Orbis” using the FDA Assessment Aid and no TGA clinical evaluation report was available. Project Orbis is an initiative of the FDA Oncology Center of Excellence, which provides a framework for concurrent submission and review of oncology drugs among international partners. The FDA approved NIVO+IPI as first-line treatment for adult patients with unresectable MPM in Oct 2020.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
NIVOLUMAB 100 mg/10 mL injection, 10 mL vial 40 mg/4 mL injection, 4 mL vial	360 mg	13 (initial and continuing treatment)	Published price	Opdivo® Bristol-Myers Squibb Australia Pty Ltd
			\$7,562.08 public hospital	
			\$7,707.37 private hospital	
			Effective price	
			\$ [redacted] public hospital	
			\$ [redacted] private hospital	

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Medicare; retrospective audit of patient records possible)
Severity: Unresectable
Condition: Malignant pleural mesothelioma
Indication: Unresectable malignant pleural mesothelioma
Clinical criteria: Patient must not have received prior treatment with a programmed cell death 1 (PD-1) inhibitor or a programmed cell death ligand 1 (PD-L1) inhibitor for this condition.
AND Patient must have an Eastern Cooperative Oncology Group (ECOG) a WHO performance status of 0 or 1.
AND The treatment must be in combination with PBS-subsidised ipilimumab, unless an intolerance to ipilimumab of a severity necessitating permanent treatment withdrawal of ipilimumab
AND

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Patient must not have developed disease progression while being treated with this drug for this condition
AND
The treatment must not exceed a maximum total of 24 months in a lifetime for this condition.
Administrative Advice: Patients who have developed intolerance to ipilimumab of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised nivolumab
Administrative Advice: No increase in the maximum number of repeats may be authorised
Administrative Advice: Special Pricing Arrangements apply
Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.
CAUTION: Combination treatment with ipilimumab and nivolumab is associated with an increased incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.
No increase in the maximum number of repeats may be authorised.

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
IPILIMUMAB 50 mg/10 mL injection, 10 mL vial	120 mg	4 (initial and continuing treatment)	Published price	Yervoy® Bristol-Myers Squibb Australia Pty Ltd
			\$16,963.54 public hospital	
			\$17,240.45 private hospital	
			Effective price	
			\$ [redacted] public hospital	
\$ [redacted] private hospital				

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Medicare; retrospective audit of patient records possible)
Severity: Unresectable
Condition: Malignant pleural mesothelioma
Indication: Unresectable malignant pleural mesothelioma
Clinical criteria: Patient must not have received prior treatment with ipilimumab for this condition.
AND
Patient must have an Eastern Cooperative Oncology Group (ECOG) a WHO performance status of 0 or 1.
AND
The treatment must be in combination with PBS-subsidised nivolumab
AND
Patient must not have developed disease progression while being treated with this drug for this condition
AND
The treatment must not exceed a maximum total of 24 months in a lifetime for this condition.
Administrative Advice: No increase in the maximum number of repeats may be authorised
Administrative Advice: Special Pricing Arrangements apply
Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.
CAUTION: Combination treatment with ipilimumab and nivolumab is associated with an increased incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.
No increase in the maximum number of repeats may be authorised.

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- 3.2 The submission requested an effective price of \$ [REDACTED] per 100 mg vial of nivolumab and \$ [REDACTED] per 50 mg vial of ipilimumab.
- 3.3 The requested restrictions allow patients who have developed intolerance to ipilimumab of a severity necessitating permanent treatment withdrawal to continue treatment with nivolumab monotherapy, at any time after initiation of combination therapy. The evaluation noted that although consistent with the trial protocol, only 9% patients discontinued ipilimumab early in CheckMate 743, of which 64.3% were due to adverse event(s) and 35.7% for “other” reasons. The PBAC considered allowing nivolumab monotherapy in the circumstances proposed was reasonable.
- 3.4 The requested restrictions for nivolumab and ipilimumab are broader than the CheckMate 743 trial and the proposed TGA indication, as they do not state that NIVO+IPI should only be used in the first-line setting. The submission argued that given the lack of standard of care or recognised second-line treatment options in patients that have experienced disease progression following first-line systemic treatment the broader PBS restriction would allow patients with otherwise limited efficacious treatment options to access NIVO+IPI. The PBAC considered it was reasonable to not specify first line treatment in the restriction criteria.
- 3.5 The submission did not indicate whether there would be patient access program prior to PBS listing for NIVO+IPI and a grandfather provision was also not included in the requested restriction. The Pre-Sub-Committee Response (PSCR) stated that while there is currently no formal patient access program for NIVO+IPI in MPM, and no plans to open one, the Sponsor has granted compassionate access in response to requests made since April 2020. The pre-PBAC response stated there were currently < 500 patient actively receiving compassionate access to NIVO+IPI and these should be added to the financial estimates, taking into account treatment already received. The PBAC noted a separate restriction criteria is not required as these patients should meet the restriction criteria outlined in Section 8.
- 3.6 The submission stated that the proposed number of repeats for nivolumab (13) was to facilitate at least six months of treatment whether nivolumab is administered at a flat dosing regimen of 360 mg Q3W or using a weight-based dosing regimen of 3 mg/kg Q2W. The PBAC considered the restriction criteria should be amended to 8 repeats (which allows for 24 weeks of treatment with the flat dosing regimen) with a note to allow an increase in repeats for patients being treated with the weight-based dosing regimen. The PBAC noted the number of repeats for ipilimumab should be reduced to 3 to allow for 24 weeks of treatment.

For more detail on PBAC’s view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Malignant mesothelioma is a relatively rare and insidious neoplasm. It arises from mesothelial surfaces of the pleural cavity, peritoneal cavity, tunica vaginalis, or pericardium. MPM is the most common type of malignant mesothelioma and mostly occur in patients aged 60 years and older. It typically presents decades after an exposure to asbestos with gradually worsening, nonspecific pulmonary symptoms such as chest pain, dyspnoea, cough, hoarseness, or dysphagia, which occur in the setting of extensive intrathoracic disease.
- 4.2 Mesothelioma can be divided into three histologic subtypes, epithelioid (about 60% of cases), sarcomatoid (10 to 20%) and a combination of epithelioid and sarcomatoid known as biphasic (about 30%)¹. The survival of people with malignant pleural mesothelioma is typically around one year, with improved outcomes for people who have the epithelioid subtype or are surgically treated. People who have the sarcomatoid subtype have poorer outcomes overall with survival around 4 months, regardless of surgical status². Other poor prognostic indicators include, stage of disease, poor performance status, age >75 years, elevated lactate dehydrogenase (LDH), and haematologic abnormalities. The majority of affected patients die from local extension and respiratory failure.
- 4.3 The submission proposed two populations:
- First-line setting for patients with a confirmed diagnosis of MPM who are not suitable for surgical resection; and
 - Second-line setting for the cohort of patients who initiated treatment with pemetrexed-based chemotherapy prior to the PBS availability of NIVO+IPI for first-line MPM. However, the requested restriction did not specifically limit use to second-line and patients could potentially use NIVO+IPI in any line.
- 4.4 The proposed clinical algorithm indicated that all patients diagnosed with unresectable MPM will receive first-line treatment with NIVO+IPI. Following this, patients receive pemetrexed-based chemotherapy, best supportive care (BSC) or enter into a clinical trial. The proposed clinical algorithm did not account for the proportion of patients who may not be suitable or eligible for NIVO+IPI, patients who may not tolerate ipilimumab (and therefore continue with nivolumab monotherapy), and existing patients who have experienced disease progression following first-line treatment with pemetrexed-based chemotherapy.

¹ van Zandwijk N, Clarke C, Henderson D et al. (2013) Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. *Journal of Thoracic Disease* 5(6), E254–E307.

² Meyerhoff RR, Yang CJ, Speicher PJ et al. (2015) Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database. *Journal of Surgical Research* 196(1), 23–32.

- 4.5 Some publications³ have recently recommended NIVO+IPI as first-line treatment for non-epithelioid histology only, and pemetrexed plus cisplatin for patients with epithelioid MPM (based on CheckMate 743 subgroup analyses; see paragraphs 6.14–6.15). However, NIVO+IPI was recommended as a reasonable alternative in epithelioid MPM, particularly for patients unable to tolerate pemetrexed-based chemotherapy. It is recognised however that CheckMate 743 was not powered to compare OS between NIVO+IPI and pemetrexed-based chemotherapy in histologic subgroups, and that there are inherent limitations to the interpretation of subgroup results.
- 4.6 Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. Nivolumab potentiates T-cell responses, including anti-tumour responses, by blocking PD-1 from binding to PD-L1 and PD-L2 ligands and restoring the immune response against the tumour. Ipilimumab is a fully human monoclonal antibody which binds to the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). By blocking T-cell inhibitory signals induced by the CTLA-4 pathway, ipilimumab increases the number of tumour reactive T effector cells able to mount a direct T-cell immune attack against tumour cells. The two drugs work synergistically to increase immune response against tumours.
- 4.7 The dosing of nivolumab when used in combination with ipilimumab in CheckMate 743 was 3 mg/kg Q2W. However, the proposed dosing regimen in the draft TGA Product Information (PI) was 3 mg/kg Q2W or a flat dose of 360 mg every three weeks (Q3W). The TGA Delegate considered the available evidence adequately supported a nivolumab dose of 360 mg every 3 weeks as an alternative dose to 3mg/kg every 2 weeks.

5 Comparator

- 5.1 The submission nominated pemetrexed-based chemotherapy as the main comparator in the first-line setting. The main arguments provided in support of this nomination were that local and international clinical guidelines recommend a combination chemotherapy regimen containing pemetrexed and a platinum compound as a first line treatment option for patients with MPM. The submission reasoned that pemetrexed and cisplatin or carboplatin are also the most likely PBS listed regimen to be replaced if NIVO+IPI became PBS listed.
- 5.2 The submission nominated BSC, including pemetrexed rechallenge, as a supplementary comparator, in the context where patients experience disease progression following first-line pemetrexed-based chemotherapy treatment. The

³ Systemic treatment for unresectable malignant pleural mesothelioma; UpToDate, accessed 5 Jan 2021: https://www.uptodate.com/contents/systemic-treatment-for-unresectable-malignant-pleural-mesothelioma?search=mesothelioma&source=search_result&selectedTitle=4~86&usage_type=default&display_rank=4#H4259687384

rationale in support of this was that clinical guidelines describe a role for pemetrexed rechallenge in some patients. Currently, there is no single standard of care recommended for patients who progress following first-line systemic treatment.

- 5.3 In CheckMate 743, 48% of NIVO+IPI patients and 45% of pemetrexed-based chemotherapy patients received any subsequent therapy. Of those who received subsequent therapy, 90% of NIVO+IPI patients and 70% of pemetrexed-based chemotherapy patients received systemic chemotherapy. Therefore, for a proportion of patients, the availability of NIVO+IPI may represent an additional line of therapy; i.e. NIVO+IPI may displace rather than replace chemotherapy. The submission's economic and financial analyses did not take these considerations into account.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician described their favourable experience of using NIVO+IPI for MPM patients, and noted it is generally well-tolerated with similar outcomes observed in patients with epithelioid and non-epithelioid histology, in contrast to chemotherapy where inferior outcomes are observed in patients with non-epithelioid histology.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (5), health care professionals (8) and organisations (7) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with NIVO+IPI including a survival benefit, improved quality of life and a perception of better tolerability than chemotherapy. Many of the comments discuss the importance of having additional treatment options available for patients with MPM. A number of comments from health care professionals acknowledged the larger benefit in patients with non-epithelioid histology where current treatment is generally ineffective, compared to those with epithelioid histology.
- 6.3 The PBAC noted input was received from Asbestos Victims Association (SA), Asbestos Council of Victoria, Asbestos Diseases Research Institute, Lung Foundation Australia, Asbestos Diseases Society of Australia and Rare Cancers Australia. The submissions described the significant impact of mesothelioma on patients and the lack of new treatment options over the last decade.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the NIVO+IPI submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the CheckMate 743 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical

Benefit Scale (ESMO-MCBS) for NIVO+IPI, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement).⁴

Clinical trials

6.5 First-line setting: the submission was based on one randomised, open-label, head-to-head trial comparing NIVO+IPI (N=303) to pemetrexed-based chemotherapy (N=302) in patients with unresectable MPM without any prior treatment (CheckMate 743).

6.6 Second- or later-line setting: the comparison of NIVO+IPI versus BSC (including pemetrexed rechallenge) was based on a naïve indirect comparison using the following three studies:

- MAPS2: a randomised, open-label trial comparing nivolumab monotherapy (N=68) to NIVO+IPI (N=64) in MPM patients with disease progression after one to two lines of systemic chemotherapy
- INITIATE: a single-arm trial of NIVO+IPI (N=35) in MPM patients with disease progression or recurrence after at least one line of platinum-containing systemic therapy
- Jassem 2008: a randomised trial comparing pemetrexed plus BSC (N=123) to BSC alone (N=120) in previously treated MPM patients with disease progression after one line of systemic chemotherapy

6.7 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CheckMate 743: NCT02899299	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. Baas P, Scherpereel A, Nowak A et al. First-line nivolumab + ipilimumab vs chemotherapy in unresectable malignant pleural mesothelioma: Checkmate 743	August 2020* <i>Journal of Thoracic Oncology</i> 2020; 15(10):p.e42
MAPS2: NCT02716272	Scherpereel A, Mazieres J, Greillier L et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS): A multicentre, open-label, randomised, non-comparative, phase 2 trial	<i>The Lancet Oncology</i> 2019; 20: 239-253.
INITIATE: NCT03048474	Disselhorst M, Quispel-Janssen J, Lalezari F et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): Results of a prospective, single-arm, phase 2 trial.	<i>The Lancet Respiratory Medicine</i> 2019; 7: 260-270.
Jassem 2008	Jassem J, Ramlau R, Santoro A et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma.	<i>Journal of Clinical Oncology</i> 2008; 26(10): 1698-1704.

Only main publications have been reported in this table.

Source: Tables 16-17, pp.48-49 of the submission.

* Full publication occurred during evaluation: *Lancet* 2021; 397(10272):375-386.

⁴ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

6.8 The key features of the included evidence are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
First-line setting						
NIVO+IPI versus pemetrexed-based chemotherapy						
CheckMate 743	605	R, OL, MC 22 mths ^a	Moderate, but low for OS ^c	Unresectable MPM without prior treatment	OS, PFS	Used
Second- or later-line setting						
NIVO+IPI (non-comparative) – second or later-line						
MAPS2	64 ^b	R ^d , OL, MC 20 mths	High ^e	MPM, disease progression after 1-2 lines of prior systemic chemo	OS, PFS, disease control	Not used
INITIATE	35	Single arm 14 mths	High ^f	MPM, disease progression or recurrence after ≥ 1 line of prior systemic chemo	OS, PFS, disease control	Not used
Pemetrexed+BSC versus BSC - second-line						
Jassem 2008	243	R, OL, MC 15 mths	High ^g	MPM, disease progression after 1 line of prior systemic chemo excluding pemetrexed	OS, PFS, time to tumor progression	Not used

^a Minimum follow-up for overall survival was 22.1 months (calculated as time from last subject's randomisation date (22 May 2018) to 25 March 2020 (the trial's clinical cut-off date for OS). Median follow-up for OS was 29.7 months for all randomised subjects (calculated as median time from randomisation date to the clinical data cut-off for OS (ie, 25 March 2020) (Table S.5.3 and pp21 and 83 of CheckMate 743 CSR).

^b Number of patients randomised to the NIVO+IPI treatment group only.

^c CheckMate 743: Open-label, OS could be influenced by the subsequent use of immunotherapies. 47.9% and 45.0% of NIVO+IPI and pemetrexed-based chemotherapy patients, respectively, received subsequent treatments.

^d Patients were randomised 1:1 to received NIVO or NIVO+IPI, but there were no formal statistical comparison across the two groups.

^e MAPS2: Open-label, NIVO+IPI not compared to relevant comparator.

^f INITIATE: Open-label, single-arm. NIVO dose 240 mg Q2W

^g Jassem 2008: Open-label, non-comparative study of comparator (pemetrexed); unclear whether the response and PFS assessments were blinded to radiologists.

DB, double blind; MC, multi-centre; OL, open label; OS, overall survival; PFS, progression-free survival; R, randomised;

BSC, best supportive care; chemo, pemetrexed plus cisplatin/carboplatin; IPI, ipilimumab; MPM, malignant pleural mesothelioma; NIVO, nivolumab.

Source: constructed during the evaluation.

6.9 The Jassem 2008 study assessed the use of pemetrexed in patients that had received treatment with one prior systemic chemotherapy regimen, excluding pemetrexed. Hence, the Jassem 2008 patients had not received the current standard of care, which is first-line treatment of pemetrexed-based chemotherapy. As such, results from Jassem 2008 has limited applicability to the PBS setting and patients are not comparable to those in MAPS2 and INITIATE.

- 6.10 Three additional systematic reviews of second line therapies in MPM (Petrelli 2018⁵; Abdel-Rahman 2015⁶; Buikhuisen 2015⁷) were identified during the evaluation, from which additional potentially relevant studies of pemetrexed rechallenge in second-line use (other than Jassem 2008) were identified. These studies included patient populations relevant to the proposed PBS listing for second-line use, i.e., second-line use of pemetrexed in patients treated with first-line pemetrexed-based chemotherapy (Zucali et al., 2012⁸; Bearz et al., 2012⁹). Overall survival reported in these studies indicated potentially higher OS with second-line pemetrexed than reported by Jassem 2008.
- 6.11 All the included evidence were open-label studies. The submission's clinical claim was based on OS from direct comparisons in first-line use, and naïve unadjusted indirect comparisons in second-line use. The risk of bias for the key outcome of OS was considered to be low, however, the OS results were potentially confounded by the subsequent use of immunotherapies which was permitted in the CheckMate 743 trial.

Comparative effectiveness

- 6.12 The key primary and secondary results for the CheckMate 743 trial is presented below.

⁵ Petrelli F, Ardito R, Conti B et al. A systematic review and meta-analysis of second-line therapies for treatment of mesothelioma. *Respiratory Medicine* 2018; 141: 72-80.

⁶ Abdel-Rahman, O and Kelany M. Systemic therapy options for malignant pleural mesothelioma beyond first-line therapy: a systematic review. *Expert Review of Respiratory Medicine* 2015; 9(5): 533-549.

⁷ Buikhuisen W, Hiddinga B, Baas P et al. Second line therapy in malignant pleural mesothelioma: A systematic review. *Lung Cancer* 2015; 89: 223-231.

⁸ Zucali P, Simonelli M, Michetti G et al. Second-line chemotherapy in malignant pleural mesothelioma: Results of a retrospective multicentre survey. *Lung Cancer* 2012; 75: 360-367.

⁹ Bearz A, Talamini R, Rossoni G et al. Re-challenge with pemetrexed in advanced mesothelioma: a multi-institutional experience. *BMC Research Notes* 2012; 5: 482.

Table 4: Key results of outcomes in CheckMate 743 (ITT)

Outcomes		NIVO+IPI; N=303	Chemo; N=302
Primary			
OS	Patients with event, n (%)	200 (66.0)	219 (72.5)
	Median (95% CI), months	18.07 (16.82, 21.45)	14.09 (12.45, 16.23)
	HR ^a (95% CI), p-value	0.74 (0.61, 0.89), p=0.0020	
Secondary/other			
PFS per BICR, primary definition ^b	Patients with event, n (%)	218 (71.9)	209 (69.2)
	Median (95% CI), months	6.77 (5.59, 7.36)	7.20 (6.93, 8.05)
	HR ^a (95% CI), p-value	1.00 (0.82, 1.21)	
ORR per BICR	ORR (95% CI), %	39.6 (34.1, 45.4)	42.7 (37.1, 48.5)
	Median TTR, months	2.69	2.53
	DoR (95% CI), months	11.01 (8.11, 16.49)	6.67 (5.32, 7.10)
BOR, n(%)	CR	5 (1.7)	0
	PR	115 (38.0)	129 (42.7)
	SD	112 (37.0)	125 (41.4)
	PD	55 (18.2)	14 (4.6)
DCR	(95% CI), % (CR+PR+SD)	76.6 (71.4, 81.2)	85.1 (80.6, 88.9)

^a Stratified Cox proportional hazard model.

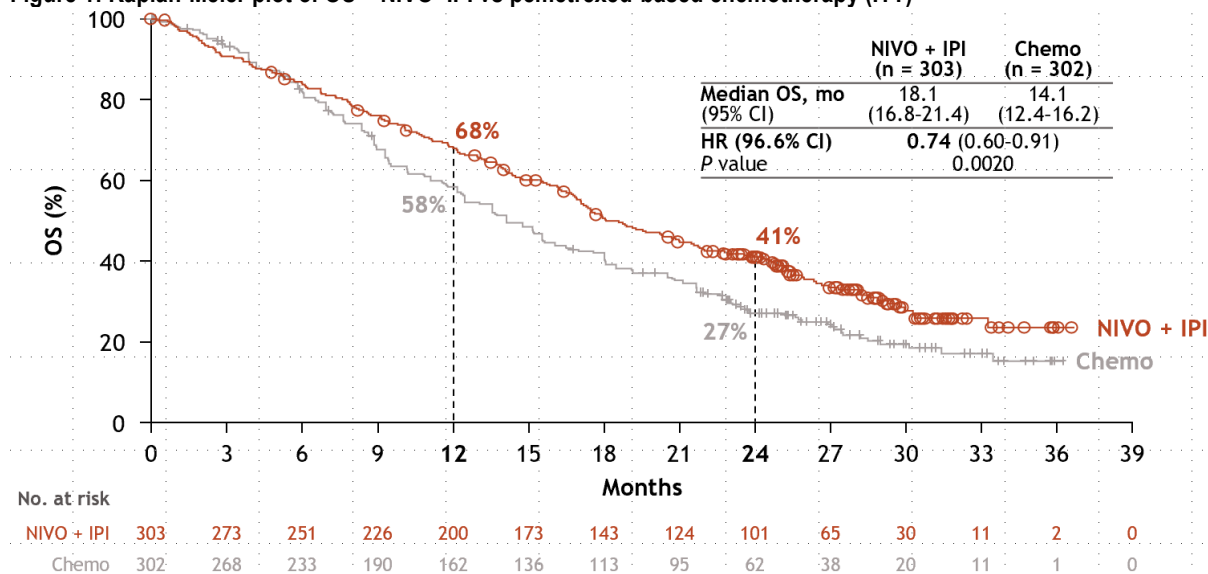
^b PFS truncated at subsequent therapy. Patients who received subsequent anticancer therapy prior to documented progression, or patients who did not have a documented progression and received subsequent anticancer therapy, were censored at the date of the last evaluable tumour assessment conducted on or prior to the date of initiation of the subsequent therapy.

Chemo, pemetrexed plus cisplatin/carboplatin; IPI, ipilimumab; NIVO, nivolumab; CI, confidence interval; HR, hazard ratio; ITT, intention to treat; BICR, blinded independent central review; BOR, best overall response; CR, complete response; DCR, disease control rate; DoR, duration of response; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.

Source: Table 7.1-1 of CheckMate 743 CSR.

6.13 The Kaplan-Meier curve for OS is presented in Figure 1. At the time of the trial analysis, 419 deaths had occurred out of a possible 605 (69%).

Figure 1: Kaplan-Meier plot of OS – NIVO+IPI vs pemetrexed-based chemotherapy (ITT)



Chemo, pemetrexed plus cisplatin/carboplatin; CI, confidence interval; IPI, ipilimumab; ITT, intention to treat; NIVO, nivolumab; OS, overall survival.

Source: Figure 15, p83 of the submission.

- 6.14 Results in Table 4 and Figure 1 illustrate that treatment with NIVO+IPI is associated with OS gains compared to pemetrexed-based chemotherapy, with better absolute survival at 6, 12, 18 and 24 months. A statistically significant difference for OS was observed for NIVO+IPI versus pemetrexed-based chemotherapy (HR 0.74, 95% CI 0.61-0.89). The improvement in median OS for NIVO+IPI versus the chemotherapy arms was 4.0 months in the ITT population.
- 6.15 After study treatment was discontinued in the CheckMate 743 trial, 134 (44.2%) of NIVO+IPI patients and 123 (40.7%) of chemotherapy patients proceeded to receive subsequent systemic therapy (Table 5). Of these patients, 10 (3.3%) NIVO+IPI patients and 61 (20.2%) chemotherapy patients, received subsequent immunotherapy. Therefore, the evaluation considered the OS results were potentially confounded by the subsequent use of systemic therapies in CheckMate 743. The ESC considered it was uncertain whether the use of subsequent therapies in the trial biased the results in favour of NIVO+IPI or pemetrexed-based chemotherapy or neither; however, considered that, overall, the use of subsequent therapies in CheckMate 743 was likely to be reasonably consistent with clinical practice.

Table 5: Subsequent therapies in CheckMate 743

	NIVO+IPI N=303	Chemo N=302
	n (%)	n (%)
Any subsequent therapy	145 (47.9)	136 (45.0)
Subsequent systemic therapy	134 (44.2)	123 (40.7)
Subsequent immunotherapy	10 (3.3)	61 (20.2)
Chemotherapy	131 (43.2)	95 (31.5)
Subsequent radiotherapy	23 (7.6)	28 (9.3)
Subsequent surgery	1 (0.3)	3 (1.0)

Chemo = pemetrexed plus cisplatin/carboplatin; NIVO = nivolumab; IPI = ipilimumab
Source: Table 32, p73 of the submission

6.16 The results of subgroup analyses for OS are presented in Table 6. The Kaplan-Meier curve for OS by histology is presented in Figure 2.

Table 6: OS outcomes in CheckMate 743 (subgroup analyses by randomisation stratification factors: histology and gender) and predefined subgroups PD-L1 expression and ECOG performance status

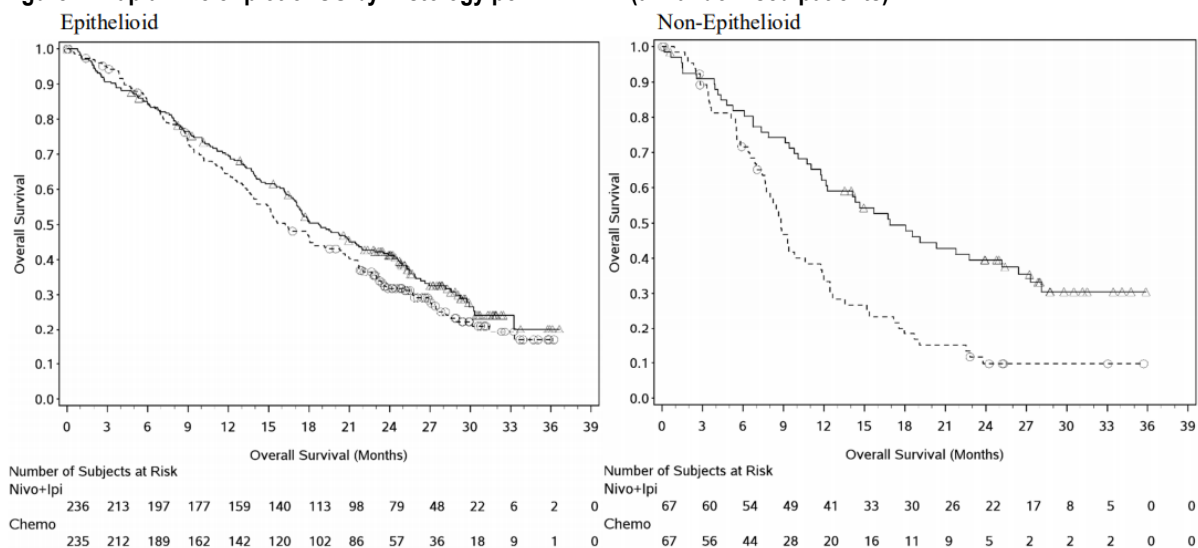
	NIVO+IPI	Chemo	NIVO+IPI	Chemo
Histology (randomisation IRT stratification factor)				
	Epithelioid		Non-epithelioid	
	N=236	N=235	N=67	N=67
Patients with event, n (%)	157 (66.5%)	164 (69.8%)	43 (64.2%)	55 (82.1%)
Median OS (95%CI), months	18.7 (17.1, 21.7)	16.2 (14.1, 19.2)	16.9 (11.8, 25.2)	8.8 (7.6, 11.8)
HR (95%CI) ^a	0.85 (0.68, 1.06)		0.46 (0.31, 0.70)	
Gender (randomisation IRT stratification factor)				
	Males		Females	
	N=235	N=234	N=68	N=68
Patients with event, n (%)	158 (67.2%)	173 (73.9%)	42 (61.8%)	46 (67.6%)
Median OS (95%CI), months	17.6 (16.2, 20.7)	13.7 (11.7, 15.5)	21.9 (14.5, 25.9)	18.0 (12.7, 23.8)
HR (95%CI) ^a	0.74 (0.60, 0.92)		0.75 (0.49, 1.15)	
PD-L1 expression (predefined subgroup; secondary endpoint)				
	<1%		≥1%	
	N=57	N=78	N=232	N=219
Patients with event, n (%)	40 (70.2%)	58 (74.4%)	150 (64.7%)	157 (71.7%)
Median OS (95%CI), months	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 (95%CI) ^a	0.94 (0.62, 1.40)		0.69 (0.55, 0.87)	
ECOG performance status (predefined subgroup)				
	0		≥1	
	N=114	N=128	N=189	N=174
Patients with event, n (%)	76 (66.7%)	81 (63.3%)	124 (65.6%)	138 (79.3%)
Median OS (95%CI), months	20.7 (17.5, 24.9)	19.5 (15.2, 22.8)	17.1 (14.1, 20.8)	11.6 (9.0, 13.9)
HR (95%CI) ^a	0.87 (0.64, 1.19)		0.66 (0.52, 0.85)	

^a Unstratified Cox proportional hazards model.

Chemo, pemetrexed plus cisplatin/carboplatin; CI, confidence interval; HR, hazard ratio; ITT, intention to treat; IRT, interactive response technology; NA, not available; ECOG, Eastern Cooperative Oncology Group; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death ligand 1.

Source: Tables 41-42, pp.84-85 of submission; Table 7.1-1, Table 7.5-1, Figure 7.2.3-1 of CheckMate 743 CSR.

Figure 2: Kaplan-Meier plot of OS by Histology per IRT – ITT (all randomised patients)



Chemo, pemetrexed plus cisplatin/carboplatin; CI, confidence interval; IPI, ipilimumab; IRT, interactive response technology; ITT, intention to treat; NIVO, nivolumab; OS, overall survival.

Source: Figure 7.2.1-1, p84 of the CheckMate 743 CSR.

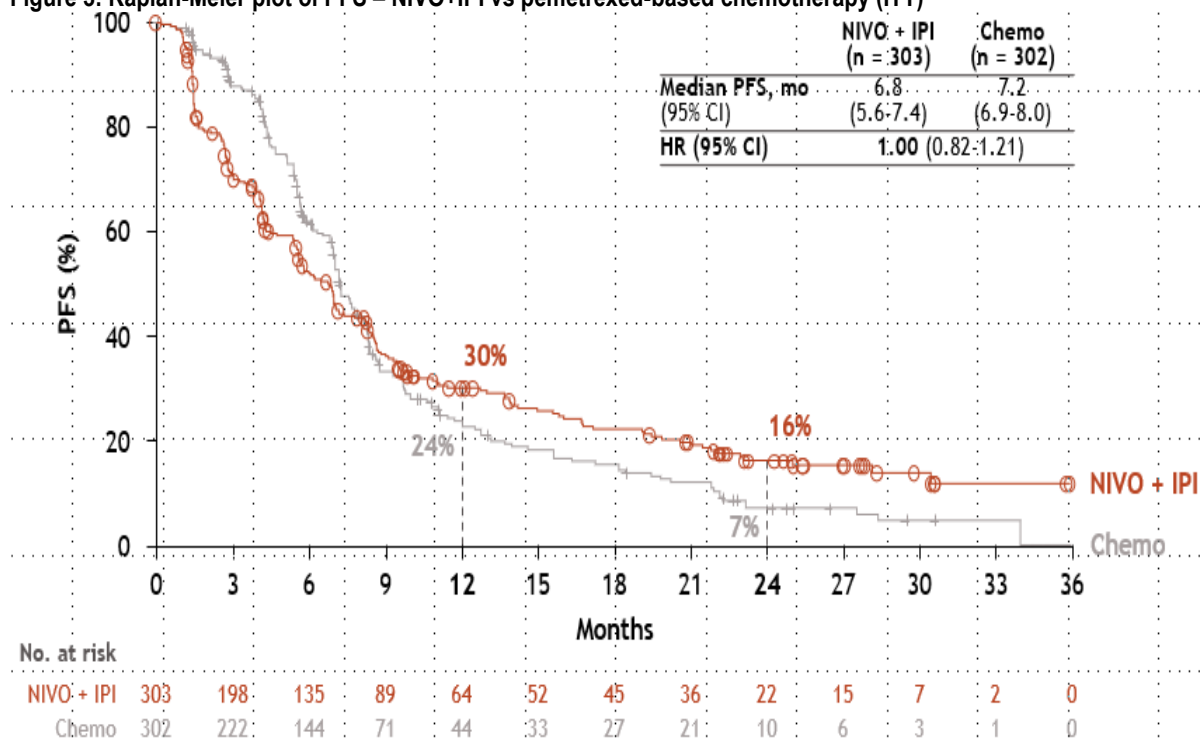
- 6.17 In CheckMate 743, randomisation was stratified according to tumour histology (epithelioid vs non-epithelioid [sarcomatoid or mixed histology subtypes]), and gender. A secondary objective was to assess whether PD-L1 expression is a predictive biomarker for the objective response rate (ORR), progression free survival (PFS), and OS.
- 6.18 The NIVO+IPI arm demonstrated statistically significant improvements in OS compared with the pemetrexed-based chemotherapy arm only for the subgroup with non-epithelioid histology (HR 0.46, 95% CI 0.31-0.70), and not for those with epithelioid histology (HR 0.85, 95% CI 0.68-1.06). The PSCR noted CheckMate 743 was not powered to detect an improvement in OS in histological subgroups. The PSCR stated the median OS in the pembrolizumab arm was similar across the histological subgroups (16.9 months in non-epithelioid, 18.7 months in epithelioid). In contrast, patients treated with chemotherapy reported substantial variation in median OS benefit (8.8 months in non-epithelioid, 16.2 months in epithelioid), consistent with histology predicting a response to chemotherapy. The ESC considered a variable response to chemotherapy did not adequately address the concerns regarding the variability of response to immune checkpoint inhibitors. PD-L1 positive tumours ($\geq 1\%$) were associated with predicted improvement with NIVO+IPI over pemetrexed-based chemotherapy (HR 0.69, 95% CI 0.55 – 0.87); while results for the complement (PD-L1 expression $<1\%$) did not reach statistical significance (HR 0.94, 95% CI 0.62, 1.40).
- 6.19 The submission claimed that the histology of patients in CheckMate 743 was consistent with Australian patients, based on data from Nowak et al. 2020 and Metaxas et al. 2018. However, based on other Australian sources reviewed during the

evaluation, the split between epithelioid and non-epithelioid histology may be more even in Australia, with the Australian Mesothelioma Registry (which has been tracking all newly diagnosed patients since 2010) reporting a split close to 50/50. The ESC considered that, in clinical practice, the proportion of patients with non-epithelioid histology was likely to be around 50%, rather than the 22% seen in CheckMate 743.

6.20 In CheckMate 743, HRs for OS favoured (HR<1) NIVO+IPI over chemotherapy in the pre-defined subgroups with the exception of subjects with age ≥75 years, Stage I/II disease, and subjects who received prior radiotherapy. These results however are not conclusive as the trial was not powered to detect OS differences in the individual subgroups. The PBAC noted that the evidence for benefit in people aged 75 years or older was highly uncertain (HR for OS 1.02 (95% CI: 0.70, 1.48)) and this was consistent with previous considerations of immunotherapy in NSCLC. The PBAC noted the median age of diagnosis for MPM in Australia was 75 years and considered the average improvement in OS of NIVO + IPI observed in CheckMate 743 may not be fully realised in clinical practice.

6.21 The Kaplan-Meier curve for PFS is presented in Figure 3.

Figure 3: Kaplan-Meier plot of PFS – NIVO+IPI vs pemetrexed-based chemotherapy (ITT)



BICR, blinded independent central review; Chemo, pemetrexed plus cisplatin/carboplatin; CI, confidence interval; IPI, ipilimumab; ITT, intention to treat; NIVO, nivolumab; PFS, progression-free survival.

Source: Figure 12, p87 of the submission.

6.22 Median PFS as assessed by BICR, truncated at subsequent therapy (primary definition) was similar between treatment groups (6.8 months versus 7.2 months for NIVO+IPI and pemetrexed-based chemotherapy, respectively) (HR 1.00, 95% CI 0.82-1.21). No statistically significant difference for PFS was observed. The Kaplan-Meier curves for

PFS showed an advantage for chemotherapy during the initial part of the curve with the curves crossing at approximately 8 months and then subsequently favouring NIVO+IPI.

- 6.23 Objective response rate (ORR) was similar between both treatment arms. The disease control rate (DCR) was lower for NIVO+IPI compared to pemetrexed-based chemotherapy. While the median time to response was similar for NIVO+IPI and pemetrexed-based chemotherapy, the duration of response was longer for NIVO+IPI compared with pemetrexed-based chemotherapy (11.0 months versus 6.7 months).
- 6.24 Improvements were observed in HRQoL for NIVO+IPI patients over those who received pemetrexed-based chemotherapy, as measured by the EQ-5D-3L utility index and VAS scores, and LCSS-Meso (mesothelioma adaptation of the Lung Cancer Symptom Score) scales. However, the HRQoL results were informed by very small patient numbers over time. There were no consistent long-term utility difference across the various HRQoL outcome measures, and these results are not considered conclusive.
- 6.25 The results for OS and PFS in the second- or later-line studies are presented in the table below.

Table 7: Summary of OS results from second- or later-line studies (first-line CheckMate 743 included for comparison purposes)

Outcome	1 st line	2 nd or later-line evidence				
	CheckMate 743	MAPS2		INITIATE	Jassem 2008	
	NIVO+IPI N=303	NIVO+IPI N=62	NIVO mono N=63	NIVO+IPI N=34	Pemetrexed + BSC N=123	BSC N=120
Median follow-up	29.7 months ^c	20.1 months		14.3 months	14.5 months	
Patients died at data cut-off ^a	200/303 (66.0%)	32/62 (51.6%)	41/63 (65.1%)	13/34 (38.2%)	NR	NR
12-month OS rate (95% CI)	67.9 (62.3, 72.8)	58.1 (45.8, 70.3)	49.2 (36.9, 61.6)	64 (50, 83)	NR	NR
Median OS months (95% CI)	18.1 (16.8, 21.5)	15.9 (10.7, NR)	11.9 (6.7, 17.7)	NR (12.7, NR)	8.4 (6.2, 10.5)	9.7 (8.4, 10.9)

Grey shading: nivolumab monotherapy, presented here for completeness.

^a MAPS2: 28th December 2017; INITIATE: 1st June 2018.

^b Jassem 2008 used the Southwest Oncology Group criteria whilst all the other included studies used mRECIST criteria.

^c calculated as median time from randomisation date the clinical data cut-off for OS (ie, 25 March 2020).

IPI, ipilimumab; NIVO, nivolumab; NR, not reached; OS, overall survival; PFS, progression-free survival.

Source: Table 51, Tables 54-55, pp.94-98 of the submission; Table 2 of Jassem 2008, p247 of MAPS2 publication; INITIATE publication.

- 6.26 In second- or later-line use, in the absence of a common comparator arm, the submission presented a naïve unadjusted indirect comparison of NIVO+IPI versus pemetrexed + BSC or BSC, for the outcome of OS. The indirect comparison of OS is presented in the table below.
- 6.27 The second-line patients in the Jassem 2008 study had not received the current standard of care, which is first-line treatment of pemetrexed-based chemotherapy.

6.28 A reasonable amount of heterogeneity was observed between trials in the second-line setting:

- A higher proportion of NIVO+IPI patients in MAPS2 and INITIATE had epithelioid histology compared to BSC patients in Jassem 2008 (approx. 85% versus approx. 72%). This has the potential to confound the results from Jassem 2008.
- The NIVO+IPI patients in MAPS2 and INITIATE tended to be older than the BSC patients in Jassem 2008.
- The best supportive trial Jassem 2008 was conducted at least 8-10 years before the NIVO+IPI trials (MAPS2 and INITIATE). During this period of time, diagnosis and treatment of MPM has changed.

Table 8: Results of the naive indirect comparison for the outcome of median OS (months) – second- or later-line setting

Trial	NIVO+IPI Median OS (95% CI)		Common reference
MAPS2	15.9 (10.7, NR)		NA
INITIATE	NR (12.7, NR)		NA
Comparators	Pemetrexed + BSC Median OS (95% CI)	BSC Median OS (95% CI)	Common reference
Jassem 2008	8.4 (6.2, 10.5)	9.7 (8.4, 10.9)	NA

BSC, best supportive care; IPI, ipilimumab; NIVO, nivolumab; NA, not available; NR, not reported, OS, overall survival.
Source: Table 58, p102 of the submission.

Comparative harms

6.29 The key AEs occurring in the CheckMate 743 trial are summarised in the table below.

Table 9: Summary of key adverse events in CheckMate 743

	NIVO+IPI N=300 n (%)	chemo N=284 n (%)	RR (95% CI)	RD (95% CI)
AEs				
Any Grade	299 (99.7)	277 (97.5)	<i>1.02 (1.00, 1.04)</i>	<i>0.02 (0.00, 0.04)</i>
Grade 3-4	159 (53.0)	121 (42.6)	<i>1.24 (1.05, 1.48)</i>	<i>0.10 (0.02, 0.18)</i>
Serious AEs				
Any Grade	164 (54.7)	72 (25.4)	<i>2.16 (1.72, 2.70)</i>	<i>0.29 (0.22, 0.37)</i>
Grade 3-4	103 (34.3)	54 (19.0)	<i>1.81 (1.36, 2.40)</i>	<i>0.15 (0.08, 0.22)</i>
Treatment-related serious AEs				
Any Grade	64 (21.3)	22 (7.7)	<i>2.75 (1.74, 4.35)</i>	<i>0.14 (0.08, 0.19)</i>
Grade 3-4	46 (15.3)	17 (6.0)	<i>2.56 (1.50, 4.36)</i>	<i>0.09 (0.04, 0.14)</i>
AEs leading to discontinuation^a				
Any Grade	88 (29.3)	58 (20.4)	<i>1.44 (1.08, 1.92)</i>	<i>0.09 (0.02, 0.16)</i>
Grade 3-4	59 (19.7)	28 (9.9)	<i>1.99 (1.31, 3.03)</i>	<i>0.10 (0.04, 0.15)</i>
Treatment-related AEs leading to discontinuation^b				
Any Grade	69 (23.0)	45 (15.8)	<i>1.45 (1.03, 2.04)</i>	<i>0.07 (0.01, 0.14)</i>
Grade 3-4	45 (15.0)	21 (7.4)	<i>2.03 (1.24, 3.32)</i>	<i>0.08 (0.03, 0.13)</i>
Deaths				
Within 30 days of last dose	28 (9.3)	14 (4.9)	<i>1.89 (1.02, 3.52)</i>	<i>0.04 (0.00, 0.09)</i>
Within 100 days of last dose	55 (18.3)	50 (17.6)	<i>1.04 (0.74, 1.47)</i>	<i>0.01 (-0.06, 0.07)</i>
Deaths by primary reason				
Deaths due to disease	183 (61.0)	199 (70.1)	<i>0.87 (0.77, 0.98)</i>	<i>-0.09 (-0.17, -0.01)</i>
Deaths due to study drug toxicity	3 ^c (1.0)	1 ^d (0.4)	<i>2.84 (0.30, 27.14)</i>	<i>0.01 (-0.01, 0.02)</i>

Figures in italics were calculated during the evaluation.

^aExposure-adjusted AEs leading to discontinuation incidence rates (per 100 person-years) were 47.7% and 76.2% for NIVO+IPI and chemotherapy, respectively (CheckMate 743 CSR).

^bExposure-adjusted treatment-related AEs leading to discontinuation incidence rates (per 100 person-years) were 37.7% and 59.2% for NIVO+IPI and chemotherapy, respectively (CheckMate 743 CSR).

^cCauses of death: pneumonitis, toxicity of immunotherapy and development of neurological complications, and acute heart failure.

^dCause of death myelosuppression due to drugs and salmonella sepsis.

AE, adverse event; Chemo, pemetrexed plus cisplatin/carboplatin; CI, confidence interval; IPI, ipilimumab; NIVO, nivolumab; n, number of participants reporting data; N, total participants in group; RD, risk difference; RR, relative risk.

Source: Table 60, p104 of submission; Table 8.1-1, p110 of CSR.

6.30 In Checkmate 743, higher proportions of patients treated with NIVO+IPI compared to chemotherapy experienced Grade 3-4 AEs and serious AEs (regardless of causality), as well as treatment related serious AEs and AEs leading to discontinuation (treatment related and regardless of causality). However, incidence rates of exposure-adjusted AEs leading to discontinuation were lower in the NIVO+IPI arm compared to the pemetrexed based chemotherapy arm.

6.31 The use of NIVO+IPI was associated with an increased rate of immune-mediated adverse events (IMAEs). The proportion of patients with diarrhoea/colitis, hepatitis, pneumonitis, rash, hypophysitis, hypothyroidism and hyperthyroidism was higher for NIVO+IPI versus pemetrexed-based chemotherapy. Most IMAEs were Grade 1-2, with the exception of hepatitis and nephritis/ renal dysfunction. Overall, the nature of

these IMAEs was consistent with the established IMAE profile of immunotherapy-based treatment regimens.

6.32 A comparison of key adverse events across the second or later-line NIVO+IPI and pemetrexed and BSC studies is provided in the table below.

Table 10: Summary of key adverse events in MAPS2, INITIATE and Jassem 2008

	MAPS2		INITIATE	Jassem 2008	
	NIVO mono N=63 n (%)	NIVO+IPI N=61 n (%)	NIVO+IPI N=35 n (%)	Pemetrexed + BSC N=123 n (%)	BSC N=120 n (%)
Treatment-related AEs					
Any Grade	56 (88.9)	57 ^b (93.4)	33 (94.3)	NR	NR
Grade 3-4	9 (14.3)	16 (26.2)	13 (37.1)	NR	NR
Treatment-related Serious AEs					
Any Grade	3 (4.8)	14 (23.0)	5 (14.3)	NR	NR
Grade 3-4	2 (3.2)	7 (11.5)	5 (14.3)	NR	NR
Treatment-related AEs leading to discontinuation					
Any Grade	3 (4.8)	13 (21.3)	1 (2.9)	2 (1.6) ^c	0
Grade 3-4	1 (1.6)	9 (14.8)	NR	NR	NR
Deaths due to study drug toxicity	0	3 ^a (4.9)	NR	0	0

^a Causes of death in MAPS2: one fulminant hepatitis, one encephalitis and one acute kidney failure in a patient with disease progression exhibiting recurrent pleural and peritoneal effusions needing daily punctures.

^b MAPS2: 57 reported in the text on p247 of publication, compared to 54 Grade 1-4 AEs in Table 2, p248 of publication.

^c One additional patient discontinued treatment but not treatment-related.

AE, adverse event; CI, confidence interval; IPI, ipilimumab; NIVO, nivolumab.

Source: Table 64, p109 of submission; Table 2 of MAPS2 publication.

6.33 Given the paucity of safety data reported for the Jassem 2008 study, a meaningfully robust comparison of the overall safety of NIVO+IPI versus pemetrexed and BSC could not be made.

Benefits/harms

6.34 A summary of the comparative benefits and harms for NIVO+IPI versus pemetrexed-based chemotherapy in first-line use is presented in the table below.

Table 11: Summary of comparative benefits and harms for NIVO+IPI and pemetrexed-based chemotherapy – first-line setting based on CheckMate 743 trial

Trial	NIVO+IPI n/N	Chemotherapy n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				NIVO+IPI	Chemo	
Benefits						
Overall survival (median duration of follow up 29.7 months)						
Event	NIVO+IPI		Chemotherapy	Absolute Difference		HR (95% CI)
Deaths, n/N (%)	200/303 (66.0%)		219/302 (72.5%)	6.5%		0.74 (0.61, 0.89)^a
Median OS, months (95% CI)	18.07 (16.82, 21.45)		14.09 (12.45, 16.23)	3.98		P=0.002
Harms						
	NIVO+IPI n/N	Chemotherapy n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				NIVO+IPI	Chemo	
Any Grade 3-4 AEs						
CheckMate 743	159/300	121/284	1.24 (1.05, 1.48)	53.0	42.6	0.10 (0.02, 0.18)
Serious AEs (any grade)						
CheckMate 743	164/300	72/284	2.16 (1.72, 2.70)	54.7	25.4	0.29 (0.22, 0.37)
Serious AEs (Grade 3-4)						
CheckMate 743	103/300	54/284	1.81 (1.36, 2.40)	34.3	19.0	0.15 (0.08, 0.22)
AEs leading to discontinuation (any grade)						
CheckMate 743	88/300	58/284	1.44 (1.08, 1.92)	29.3	20.4	0.09 (0.02, 0.16)
AEs leading to discontinuation (Grade 3-4)						
CheckMate 743	59/300	28/284	1.99 (1.08, 1.92)	19.7	9.9	0.10 (0.04, 0.15)

Figures in italics were calculated during the evaluation.

* Median duration of follow-up (defined as time from clinical cut-off date to all subjects' randomisation dates) was 29.7 months. Minimum follow-up 22.1 months.

^a Stratified Cox proportional hazard model.

HR, hazard ratio; PBO, placebo; RD, risk difference; RR, risk ratio; AE, adverse event; Chemo, pemetrexed plus cisplatin/carboplatin; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival.

Source Tables 39, 60, pp 82, 104 of submission, Table 8.1-1, p110 of CSR..

- 6.35 On the basis of direct comparative evidence presented by the submission, for every 100 patients treated with NIVO+IPI in comparison with pemetrexed-based chemotherapy approximately 10 additional patients will be alive after 12 months.
- 6.36 On the basis of direct comparative evidence presented by the submission, the comparison of NIVO+IPI and pemetrexed-based chemotherapy resulted in approximately a four-month improvement in overall survival over a median duration of follow-up of 29.7 months.
- 6.37 On the basis of direct comparative evidence presented by the submission, for every 100 patients treated with NIVO+IPI in comparison with pemetrexed-based chemotherapy over a median duration of follow-up of 29.7 months:
- Approximately 10 additional patients would have grade 3-4 adverse events.
 - Approximately 29 and 15 additional patients would experience serious adverse events, all grades and grades 3-4, respectively.
 - Approximately 9 and 10 additional patients would experience adverse events leading to discontinuation, all grades and grades 3-4, respectively.

- 6.38 The naïve indirect comparison presented in the submission for the second- or later-line setting did not allow for a quantitative comparison of the benefits and harms of NIVO+IPI and BSC. Accordingly, a benefits/harms table has not been presented.

Clinical claim

First-line setting

- 6.39 The submission described NIVO+IPI as superior in terms of effectiveness compared to pemetrexed-based chemotherapy. The ESC considered the therapeutic conclusion presented in the submission in regard to the comparative effectiveness of NIVO+IPI versus pemetrexed-based chemotherapy was supported by the evidence presented
- 6.40 The submission described NIVO+IPI as non-inferior in terms of safety compared to pemetrexed-based chemotherapy, with a different safety profile. The ESC considered this claim was not adequately supported. Considering the totality of the key safety outcomes, the proportions of patients experiencing any Grade 3-4 AEs and any serious AEs, treatment related serious AEs and any AEs leading to discontinuation were higher in the NIVO+IPI arm compared with the pemetrexed-based chemotherapy arm. The use of NIVO+IPI was associated with an increased rate of IMAEs.
- 6.41 The PBAC considered that the claim of superior comparative effectiveness was reasonable in the first line setting.
- 6.42 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Second- or later-line setting (patients with disease progression on first-line systemic treatment)

- 6.43 The submission described NIVO+IPI as superior in terms of effectiveness (OS) compared to BSC, including pemetrexed rechallenge. The ESC considered this claim was highly uncertain. The key issues were:
- Only non-comparative studies were identified.
 - The comparator Jassem 2008 study assessed the use of pemetrexed in patients that had received treatment with one prior systemic chemotherapy regimen, excluding pemetrexed. Hence, the patients had not received the current standard of care (first-line pemetrexed-based chemotherapy) and are therefore not representative of the potential PBS population.
 - An independent search located several other potentially relevant studies of pemetrexed rechallenge, which have reported longer OS than reported by Jassem 2008.
 - The OS data for NIVO+IPI in second- or later-line use was also limited, with only one of the studies (MAPS2 (N=62)) reaching median OS.

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- Given the limited data and low quality evidence presented in second- or later-line use (relying on naïve indirect comparison), a robust conclusion on comparative efficacy in second- or later-line use was not able to be reached.
- 6.44 The submission stated that it was unable to make a robust claim of NIVO+IPI versus BSC regarding safety, due to differential reporting of adverse events across trials. The ESC considered that, given the safety profile observed in CheckMate 743, NIVO+IPI was also likely to be of inferior safety versus BSC. The ESC noted a small number of patients treated with NIVO+IPI died from an AE in the MAPS2 study.
- 6.45 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data in the second line setting.
- 6.46 The PBAC noted no safety claim was made in the submission but agreed with the ESC that NIVO+IPI was likely to be of inferior comparative safety to BSC.

Economic analysis

- 6.47 The submission presented a partitioned survival analysis model with three health states: alive without progression (PFS), alive following progression (PD), and dead.
- 6.48 The economic evaluation presented a cost-utility analysis, with cost per life years (LY) gained also presented. A summary of the model is presented below.

Table 12: Summary of model structure, key inputs and rationale

Component	Description	Justification/comments
Type of analysis	Cost-effectiveness analysis, cost-utility analysis	Reasonable.
Outcomes	LYs and QALYs gained	Reasonable.
Treatments	NIVO+IPI vs pemetrexed-based chemotherapy (33% cisplatin, 67% carboplatin), based on the respective KM curves for TTD in CheckMate 743. Median duration of therapy 5.6 and 3.5 months for NIVO+IPI and pemetrexed-based chemotherapy respectively. Split of cisplatin and carboplatin taken from CheckMate 743.	Using trial-based TTD to model time on treatment was reasonable, however, the requested PBS restriction allows up to two years' treatment. Patients in the PBS setting may continue NIVO+IPI for longer than in the trial, particularly in the context of limited effectiveness of second-line therapies.
Methods used to generate results	Partitioned survival model	Reasonable.
Health states	Alive without progression (PFS), progressive disease (PD) and death	Reasonable.
Cycle length	1 week with half cycle correction	Reasonable.
Time horizon	10 years in the model base case vs 29.7 months median follow-up for OS in CheckMate 743.	Altogether, commencement of extrapolation at the earlier timepoints, choice of extrapolations and the
Transition probabilities	No specific transition probabilities were modelled; health state allocation determined by PFS and OS KM curves from Checkmate 743, with a different parametric extrapolation for each treatment arm from 17.35 months for NIVO+IPI and 13.27 months for pemetrexed-based chemotherapy. PFS was modelled such that it could not exceed OS.	10-year time horizon significantly favoured NIVO+IPI (see paragraphs 6.49 – 6.52). Multivariate sensitivity analysis using the OS and PFS KM data to 29.7 months for both arms, and using the Weibull (instead of log-logistic) function for the NIVO+IPI arm increased the ICER to from a base case of \$ [redacted] ¹ to \$ [redacted] ² per QALY gained (see Figure 6).

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Health related quality of life (HRQoL)	The submission estimated treatment specific utilities for PFS and PD health states from EQ-5D-3L data collected during CheckMate 743 (data only collected until progression in the pemetrexed-based chemotherapy arm) Adverse event disutilities were not modelled separately.	High risk of attrition bias in the utility estimates. No evidence was provided of a consistent long-term difference in the utility between treatment arms.
Costs	The submission estimated costs for treatment, administration, monitoring, management of adverse events, ongoing health state costs, and end of life costs.	Reasonable. Some issues with adverse event costs and exclusion of subsequent treatment costs. The absence of subsequent treatment did not favour NIVO+IPI, because if modelled as per CheckMate 743, a larger proportion of patients in the Chemo arm would receive the higher cost immunotherapies second line.
Software package	Excel 2013	Reasonable.

Source: compiled during evaluation

Abbreviations: Chemo = pemetrexed plus cisplatin/carboplatin; EQ-5D-3L = EuroQoL 5-dimension 3-level; HRQoL = health related quality of life; ICER = incremental cost-effectiveness ratio; IPI = ipilimumab; KM = Kaplan-Meier. LY = life-year; OS = overall survival; NIVO = nivolumab; PD = progressive disease; PFS = progression free survival; QALY = quality-adjusted life-year; TTD = time to treatment discontinuation

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$135,000 to < \$155,000

6.49 The model used PFS and OS KM data from CheckMate 743 to 17.35 months for NIVO+IPI and 13.27 months for pemetrexed-based chemotherapy (based on the median time between randomisation and a patient’s last known alive date or date of death per treatment arm), followed by parametric extrapolations to ten years. The ESC considered the commencement of extrapolation from these timepoints was inappropriate as they did not make full use of available KM data (see Figure 1 above) and favoured NIVO+IPI by exaggerating the survival gain over pemetrexed-based chemotherapy from the point of extrapolation (see Figure 4).

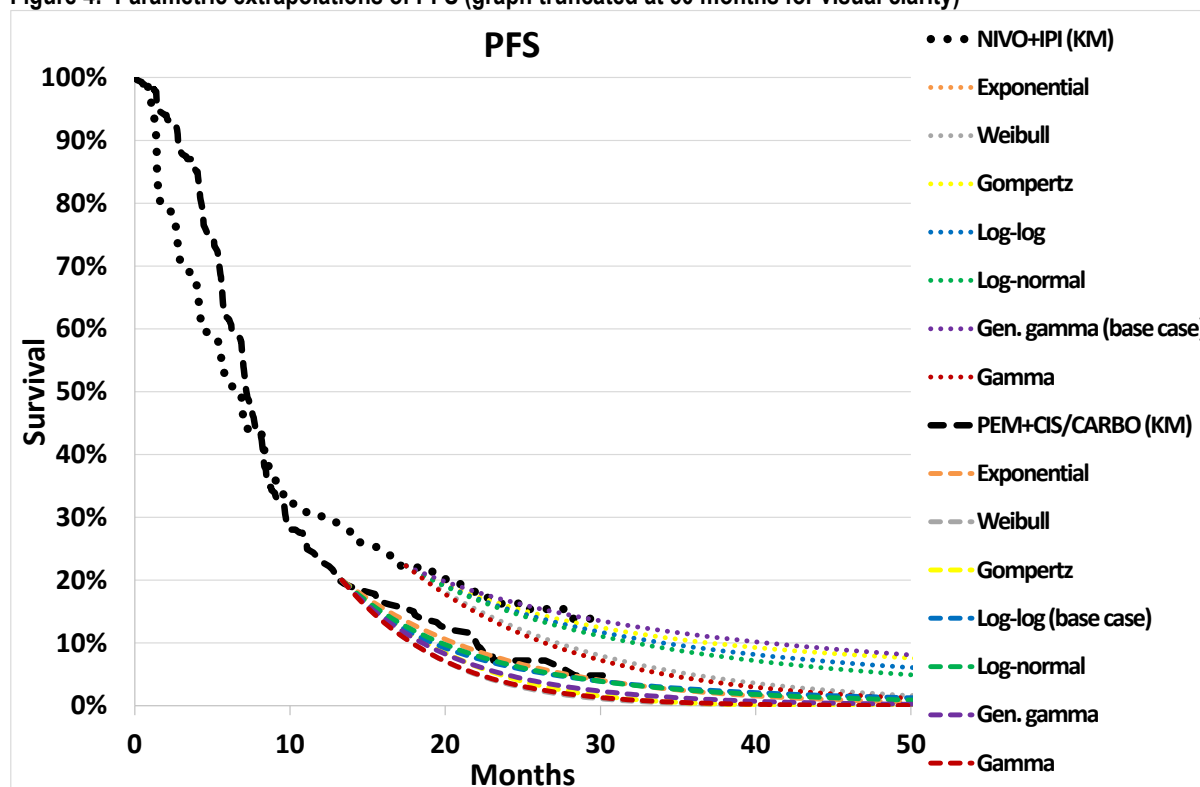
6.50 The submission presented the Grambsch and Therneau’s correlation test between Schoenfeld residuals, and log-cumulative hazard and Schoenfeld residuals plot to justify the rejection of proportional hazards assumption and the choice to fit independent parametric curves as below. Goodness of fit was determined using the Akaike information criterion (AIC) and Bayesian information criterion (BIC), along with visual inspection for the PFS curve. The submission then used the base case PFS curves to inform choice of OS extrapolation. Figures 4 and 5 present the KM data and extrapolated functions for PFS and OS.

Table 13: Summary of extrapolations used in the economic model by treatment arm and survival curve

Arm	PFS	OS
NIVO+IPI	KM to 17.35 months, then generalised gamma extrapolation	KM to 17.35 months, then log-logistic extrapolation
Chemo	KM to 13.27 months, then log-logistic extrapolation	KM to 13.27 months, then gamma extrapolation

Abbreviations: Chemo, pemetrexed+cisplatin/carboplatin; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, nivolumab; OS, overall survival; PFS, progression free survival

Figure 4: Parametric extrapolations of PFS (graph truncated at 50 months for visual clarity)



Note: KM curves truncated to 29.7 months (median OS follow up)

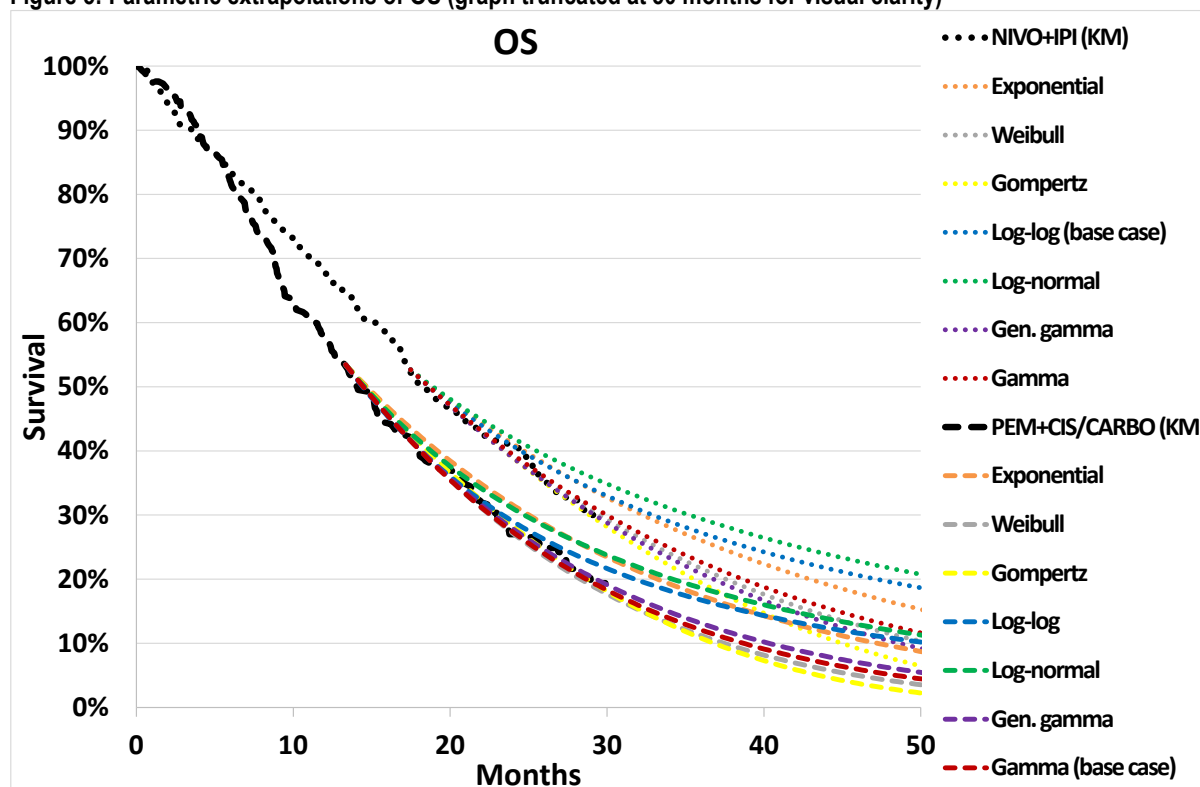
Abbreviations: CARBO, carboplatin. CIS, cisplatin; IPI, ipilimumab; KM, Kaplan-Meier; NIVO, nivolumab; PEM, pemetrexed; PFS, progression free survival

Source: Compiled during the evaluation using the Excel workbook 'Nivolumab plus Ipilimumab MPM Economic Evaluation.xlsm'

6.51 Although the choice of the generalised gamma function to extrapolate PFS for NIVO+IPI was reasonable based on AIC/BIC values, it resulted in a long tail where 3.2% of NIVO+IPI patients were estimated to be progression-free at year 10, compared to 0.2% of pemetrexed-based chemotherapy patients. This implied that some patients may be cured by NIVO+IPI, which was not supported by the clinical evidence. Using the log-logistic function to extrapolate PFS for pemetrexed-based chemotherapy also resulted in a long tail compared to other extrapolations, but this was not as pronounced as the NIVO+IPI arm, and the choice of function was reasonable based on AIC/BIC values and visual inspection. Using the choice of PFS extrapolations to inform the choice for OS extrapolations was poorly justified. Previous studies of immunotherapies in solid tumours found no significant correlation between PFS and OS¹⁰; furthermore, errors in the choice of PFS extrapolations would also carry through to the OS curves.

¹⁰ Gyawali B, Hey SP, Kesselheim AS. A Comparison of Response Patterns for Progression-Free Survival and Overall Survival Following Treatment for Cancer With PD-1 Inhibitors: A Meta-analysis of Correlation and Differences in Effect Sizes. *JAMA Netw Open*. 2018;1(2):e180416. doi:10.1001/jamanetworkopen.2018.0416

Figure 5: Parametric extrapolations of OS (graph truncated at 50 months for visual clarity)



Note: KM curves truncated to 29.7 months (median OS follow up)

Abbreviations: CARBO, carboplatin. CIS, cisplatin; IPI, ipilimumab; KM, Kaplan-Meier; OS, overall survival; NIVO, nivolumab; PEM, pemetrexed

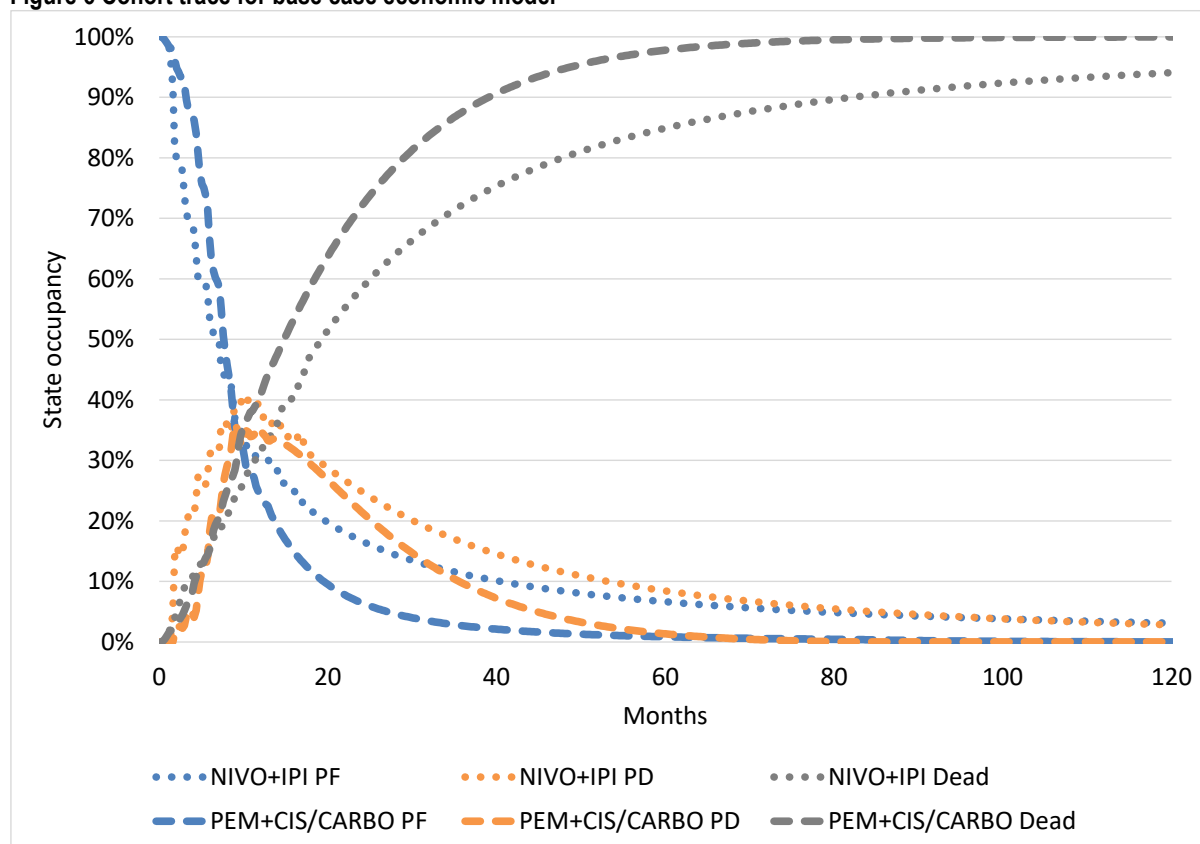
Source: Compiled during the evaluation using the Excel workbook 'Nivolumab plus Ipilimumab MPM Economic Evaluation.xlsm'

6.52 For the OS extrapolations, the base case model applied the log-logistic and gamma functions for the NIVO+IPI and pemetrexed-based chemotherapy arms respectively. However, log-logistic was ranked 6th of the parametric functions for NIVO+IPI (based on AIC/BIC) and visually overestimated the KM data from month 25 onwards. This resulted in 5.7% of NIVO+IPI patients estimated to be alive at 10 years, compared to 0.0% in the pemetrexed-based chemotherapy arm. Contrary to this, the base case model predicted 0.2% of pemetrexed-based chemotherapy patients to have not progressed at 10 years (i.e. PFS was predicted to be higher than OS). The ESC considered the proportion of patients alive at 10 years in the NIVO+IPI arm is not clinically plausible and thus highlight the inconsistency in the approach taken to choose parametric functions for the respective extrapolations. Furthermore, choice of the log-logistic extrapolation for the NIVO+IPI arm implied a sustained OS benefit, which was not supported by the clinical evidence. Based on visual inspection and AIC/BIC rankings, the evaluation considered the Weibull function demonstrated the best fit for the NIVO+IPI arm. The PSCR stated that if the Weibull function is used to extrapolate OS for the NIVO+IPI treatment arm, none of the first 4 best-fitting PFS functions are a valid choice for the NIVO+IPI arm (i.e., PFS exceeds OS from a certain

time point). The ESC considered using the choice of PFS extrapolations to inform the choice for OS extrapolations was not reasonable (paragraph 6.51).

- 6.53 Time on treatment in the model was informed by the KM data for time to treatment discontinuation (TTD) from CheckMate 743. While this was reasonable, patients in the PBS setting may continue NIVO+IPI for longer than in the trial, particularly in the context of limited effectiveness of second-line therapies and the proposed PBS restriction allowing up to 24 months of therapy. A sensitivity analysis informed by the PFS rather than TTD KM data increased the ICER from a base case of \$55,000 to < \$75,000 to \$75,000 to < \$95,000 per QALY gained. This sensitivity analysis assumed that all patients in the NIVO+IPI arm continue treatment until disease progression, death or 24 months of treatment, consistent with the proposed PBS restriction. The ESC agreed with the PSCR that using the TTD KM curve to inform time on treatment in the model was reasonable.
- 6.54 Figure 6 illustrates the model traces compiled during the evaluation for both arms. At 10 years, more than 5% of patients remain alive in the NIVO+IPI arm and half of these have remained progression-free.

Figure 6 Cohort trace for base case economic model



Abbreviations: CARBO, carboplatin; CIS, cisplatin; IPI, ipilimumab; NIVO, nivolumab; PEM, pemetrexed; PD progressive disease; PF, progression free
 Source: Compiled from Excel workbook 'Nivolumab plus Ipilimumab MPM Economic Evaluation.xlsm'

6.55 Treatment specific health state utilities were applied in the economic evaluation, according to EQ-5D-3L data collected in Checkmate 743. No evidence was presented that justified a sustained difference in utility values between the two treatment arms beyond treatment discontinuation. If the same utility estimates for the PD state are applied in both treatment arms (average across both arms in Checkmate 743) the ICER increased to \$75,000 to < \$95,000 per QALY gained if implemented from trial end (36 months), or \$75,000 to < \$95,000 per QALY gained if applied for total time in the PD state.

6.56 Table 14 provides a summary of the key drivers in the modelled economic evaluation.

Table 14: Key drivers of the model - base case: \$ [redacted]¹/QALY gained

Description	Method/Value	Impact
Time horizon	The model assumed a 10-year time horizon, vs 29.7 mth median OS follow up.	Moderate to high, favours NIVO+IPI. The ICER increased to \$ [redacted] ² /QALY gained for a 5-year time horizon.
Extrapolation	PFS and OS KM data used to 17.4 months for NIVO+IPI and 13.3 months for pemetrexed-based chemotherapy.	Moderate, favours NIVO+IPI. Increasing use of PFS and OS KM data to 29.7 months for both arms increased the ICER to \$ [redacted] ³ /QALY gained.
	Choice of log-logistic extrapolation for the NIVO+IPI OS arm.	High, favours NIVO+IPI. The ICER increased to \$ [redacted] ⁴ /QALY gained when using the best fitting OS curve for NIVO+IPI (Weibull).

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; KM, Kaplan-Meier; LY, life-year; NIVO, nivolumab; OS, overall survival; PFS, progression free survival, QALY, quality-adjusted life-year; TTD, time to treatment discontinuation

Source: compiled during the evaluation

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$95,000 to < \$115,000

³ \$75,000 to < \$95,000

⁴ \$135,000 to < \$155,000

- 6.57 The key drivers of the model were the choice of OS parametric extrapolation for the NIVO+IPI arm, the time horizon and the time at which extrapolations began. The model was moderately sensitive to the choice of utility estimates, including whether the utilities were assumed to be different between treatment arms and whether this difference persisted throughout the health states. The model was also moderately sensitive to patient weight (if varied +/-20%) and the assumption of drug wastage (zero wastage assumed in the base case).
- 6.58 The summary results of the cost-effectiveness model are presented below. The incremental QALYs demonstrate how the NIVO+IPI arm is assumed to have a sustained benefit over pemetrexed-based chemotherapy in the extrapolated section of the model, with a small comparative increase in cost. This was driven by the lower utility for pemetrexed-based chemotherapy versus NIVO+IPI in the PD health state, and the additional 0.55 life years (undiscounted) accrued in PD for the NIVO+IPI arm over the chemotherapy arm. For comparison 0.48 additional life years (undiscounted) are accrued in PFS for NIVO+IPI versus pemetrexed plus cisplatin/carboplatin.

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Table 15: Results of the stepped economic evaluation

Step and component	NIVO+IPI	PEM+CIS/CARBO	Increment
Step 1: trial-based costs and outcomes			
Costs	\$ [REDACTED]	\$32,197.31	\$ [REDACTED]
LYs	1.648	1.369	0.280
Incremental cost/extra LYs gained			\$ [REDACTED] ¹ /LY gained
Step 2: trial evidence transformed to clinical outcome			
Costs	\$ [REDACTED]	\$32,197.31	\$ [REDACTED]
QALYs	1.190	0.951	0.240
Incremental cost/extra QALYs gained			\$ [REDACTED] ¹ /QALY gained
Step 3: trial evidence transformed to clinical outcome, extrapolated to 10-year time horizon			
Costs	\$ [REDACTED]	\$35,301.90	\$ [REDACTED]
QALYs	1.678	1.028	0.650
Incremental cost/extra QALYs gained			\$ [REDACTED] ² /QALY gained

Notes: chemotherapy split was 100% pemetrexed, 33% cisplatin, 67% carboplatin as received in Checkmate 743.

Abbreviations: CARBO, carboplatin; CIS, cisplatin; IPI, ipilimumab; LY, life year; NIVO, nivolumab; PEM, pemetrexed; QALY, quality-adjusted life-year

Source: Table 96, p167 of the submission.

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$55,000 to < \$75,000

6.59 The results of key sensitivity analyses are summarised below.

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Table 16: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$ [redacted]	0.65	\$ [redacted] ¹
Time horizon (base case 10 years)			
• 5 years	\$ [redacted]	0.42	\$ [redacted] ²
• 7.5 years	\$ [redacted]	0.56	\$ [redacted] ³
Extrapolations for OS (base case NIVO+IPI log logistic, Chemo gamma)			
• NIVO+IPI log-normal	\$ [redacted]	0.67	\$ [redacted] ¹
• NIVO+IPI Weibull	\$ [redacted]	0.34	\$ [redacted] ⁴
• Chemo log-logistic	\$ [redacted]	0.49	\$ [redacted] ²
Start of OS extrapolation (base case 17.4 & 13.3 mths for NIVO+IPI and chemotherapy arms respectively)			
• End of KM	\$ [redacted]	0.52	\$ [redacted] ³
• 'Min' OS follow up (22.1mths)*	\$ [redacted]	0.60	\$ [redacted] ³
• At 29.7 mths for both NIVO+IPI and chemo arms	\$ [redacted]	0.55	\$ [redacted] ³
Convergence of OS (base case no convergence)			
• 7.5 years (from 5 years)	\$ [redacted]	0.50	\$ [redacted] ²
• 10 years (from 7.5 years)	\$ [redacted]	0.61	\$ [redacted] ³
Dosing (base case NIVO 3 mg/kg Q2W IPI 1 mg/kg Q6W)			
• NIVO flat dosing at 360mg Q3W	\$ [redacted]		\$ [redacted] ³
Patient mean weight (base case 72.75kg)		0.65	
• -20% weight	\$ [redacted]		\$ [redacted] ¹
• +20% weight	\$ [redacted]		\$ [redacted] ³
Drug wastage (base case 100% vial sharing)			
• 0% vial sharing	\$ [redacted]	0.65	\$ [redacted] ³
Time on treatment (base case TTD KM data from CheckMate 743)			
• NIVO+IPI PFS state membership (KM data to 17.4 mths then gen. gamma) capped at 24 months	\$ [redacted]	0.65	\$ [redacted] ³
Utilities (base case treatment specific PFS: 0.756 NIVO+IPI, 0.749 Chemo; PD: 0.681 NIVO+IPI, 0.622 Chemo)			
• PD same in both arms (0.655)	\$ [redacted]	0.60	\$ [redacted] ³
• Average PFS 0.753, PD 0.655 in both arms		0.59	\$ [redacted] ³
• Treatment specific until trial end then overall in PD (0.655)		0.64	\$ [redacted] ³
Multivariate analyses (MA)			
1 Weibull OS for NIVO+IPI, 29.7 month cut-off for KM data	\$ [redacted]	0.32	\$ [redacted] ⁴
2 MA1 plus utility estimates equal in PD (0.655 in both arms)	\$ [redacted]	0.28	\$ [redacted] ⁵

Note: *most conservative chosen as extrapolations with the shortest tails based on visual inspection

Abbreviations: BSA, body surface area; CARBO, carboplatin; CIS, cisplatin; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; KM, Kaplan-Meier; OS, overall survival; PD, progressive disease; PEM, pemetrexed; PFS, progression free survival, Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; QALY, quality-adjusted life-year

Source: Table 103 of the submission and compiled during the evaluation.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$95,000 to < \$115,000

³ \$75,000 to < \$95,000

⁴ \$135,000 to < \$155,000

⁵ \$155,000 to < \$255,000

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- 6.60 The sensitivity analyses indicated that the model was most sensitive to the time horizon and the approach to extrapolation. The PBAC noted the pre-PBAC response proposed an alternative scenario based on using KM data to 29.7 months, log-logistic extrapolation for OS in the NIVO+IPI arm, with curve convergence from 5 years to 10 years which resulted in an ICER of \$95,000 to < \$115,000 per QALY. The pre-PBAC response considered this scenario provided an upper range for the cost-effectiveness of NIVO+IPI in MPM. The PBAC noted converging the OS curve appropriately accounted for some of the uncertainty associated with the model time horizon and the approach to extrapolation.
- 6.61 The ESC advised inclusion of costs for subsequent lines of therapy in the economic model would have been appropriate as the outcome data implicitly include the effectiveness of subsequent therapy. However, the ESC considered that, in this case, inclusion of the cost of subsequent lines of therapy is unlikely to have a significant impact on the results of the economic modelling.
- 6.62 The ESC noted the proportion of patients with non-epithelioid MPM is likely to be higher in clinical practice than in CheckMate 743 (paragraph 6.19) and effectiveness may be greater in this population (paragraph 6.18). The ESC considered that a higher proportion of use of NIVO+IPI in non-epithelioid MPM may reduce the ICER.

Drug cost/patient/course

Table 17: Drug cost per patient for proposed and comparator drugs

	Nivolumab	Ipilimumab	Pemetrexed	Cisplatin	Carboplatin
Infusions per treatment course	17.72	6.25	5.12	5.12	5.12
DPMA per infusion	\$ [REDACTED]	\$ [REDACTED]	\$195.08	\$139.24	\$154.29
Drug cost/pt/course	\$ [REDACTED]		\$1,764.28		
Drug cost/pt/course+admin cost	\$ [REDACTED]		\$2,335.01		

Abbreviations: DPMA, dispensed price for maximum amount; pt, patient

Source: Table 95 of the submission

Notes: chemotherapy split was 100% pemetrexed, 33% cisplatin, 67% carboplatin as received in Checkmate 743.

6.63 Including administration costs the modelled economic evaluation estimated an average treatment cost for NIVO+IPI of \$ [REDACTED]. The proportional split of cisplatin and carboplatin in the model was assumed to be 33% and 67% respectively, based on usage in Checkmate 743. Changes to this split however had marginal impact on the estimated ICER/QALY, given the relatively lower costs of chemotherapy compared to NIVO+IPI.

6.64 Dosing was based on average weight (72.75kg) and BSA (1.82m²) reported from Checkmate 743. The cost of NIVO+IPI was based on 3mg/kg Q2W for nivolumab and 1mg/kg Q6W for ipilimumab (though the submission also requested nivolumab 360mg flat dosing Q3W as an alternative). The cost of chemotherapy was based on the pemetrexed dose of 500mg/m², cisplatin 75mg/m² and carboplatin 550mg Q3W.

Estimated PBS usage & financial implications

6.65 The submission was considered by the DUSC. The submission adopted an epidemiological approach to estimate the financial implications of listing, for both first- and second-line use. All second-line treatments are assumed to be administered in 2022, beyond this NIVO +IPI use is assumed to be in first-line only. The key inputs applied in the financial analysis are presented below.

Table 19: Key inputs for the financial analysis

Data	Value	Source	Comment
Eligible population			
Incident patients (1L)	Yr 1: [REDACTED] ¹ Yr 2: [REDACTED] ¹ Yr 3: [REDACTED] ¹ Yr 4: [REDACTED] ¹ Yr 5: [REDACTED] ¹ Yr 6: [REDACTED] ¹	Estimated using a mesothelioma incidence rate of 2.78 per 100,000 (AIHW CAN134 data tables). This was then applied to projected population based on ABS statistics and adjusted for PBS eligibility: - % pleural (93.32%): AIHW CAN134 data - % unresectable (93.52%) : Linton et al (2014) - ECOG 0/1 (79.39%) : Lau et al (2020)	The PBAC agreed with DUSC that an incidence rate of 3.0 per 100,000 for mesothelioma would be more reasonable. The PBAC considered it was reasonable to not exclude access for patients with non-pleural mesothelioma.
Incident patients (2L)	Yr 1: [REDACTED] ² Yr 2 onwards: N/A	As per calculations for 1L population but restricted to treatment in 2 yrs prior to NIVO+IPI becoming available on PBS (ie, 2020 and 2021). PLUS - % patients alive after 1L chemotherapy (27% and 57.7% of those diagnosed in 2020 and 2021) based on Checkmate 743 result for	The requested restriction did not limit use of NIVO+IPI to 2L treatment for a specific time period, and patients could potentially continue to use NIVO+IPI as second- or later-line treatment beyond 2022. The PBAC considered the % of patients likely to receive NIVO+IPI in the 2 nd line

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Data	Value	Source	Comment
		chemo arm in Yr2 and Yr1 of follow up respectively. - % of patients with disease progression after 1L therapy (92.8% and 76.20% of patients diagnosed in 2020 and 2021) based on Checkmate 743 result for chemo arm in Yr2 and Yr1 of follow up respectively. - % progressed on chemo and eligible to initiating 2L treatment 50% (BMS advisory board)	setting is uncertain and may also depend on tumour histology. The pre-PBAC response included an additional ² patients per year to account for patients that have relapsed after surgery.
Treatment utilisation			
Uptake rate (1L)	Yrs 1-6: 56.04% (calculated as 58.99% x 95%)	It was estimated that 53.62% currently receive systemic chemo (Kao et al. 2013). The BMS Advisory board estimated an extra 10% of patients who would otherwise have been managed with BSC would commence systemic therapy due to availability of NIVO +IPI. The submission estimated this to be 58.99% assuming a relative rather than absolute increase. BMS Advisory board estimated NIVO+ IPI will be used in 95% of eligible patients.	The DUSC considered the uptake for NIVO+IPI is likely to be underestimated, particularly in patients with non-epithelioid MPM given the substantial improvement in OS in this subgroup compared to chemo. The PBAC considered that, overall, an uptake of 58.99% across all MPM was a reasonable assumption.
Uptake rate (2L)	Yr 1: 50% Yr 2 onwards: N/A	The BMS Advisory board was informed that 41% of patients in the chemo arm of Checkmate 743 received 2L systemic therapy, based on this, the BMS Advisory Board thought 50% is likely to try NIVO+IPI in 2L.	Reasonable but may vary dependent on tumour histology.
Scripts dispensed	Yr 1: ³ Yr 2: ³ Yr 3: ³ Yr 4: ³ Yr 5: ³ Yr 6: ³	1L: assuming 17.72 doses for nivolumab and 6.25 dose for IPI per initiating patient based on mean doses in Checkmate 743 2L: assuming 12 doses of nivolumab plus 4 doses for IPI per initiating patient based on median number of doses in INITIATE (Disselhorst et al., 2019)	The requested restriction permits up to 2 years of treatment; hence trial doses may underestimate use in the PBS setting. For 2L use, mean number of infusions were not available so medians were used. Checkmate 743 results indicated that median values are likely to underestimate the number of doses.
Costs			
NIVO	\$ ³ / infusion	DPMA (effective prices) assuming an average patient weight of 72.75kg at a dose of 3mg/kg Q2W for nivolumab and 1mg/kg Q6W for ipilimumab (per Checkmate 743) and weighted by the estimated private/public hospital split.	May be underestimated as the financial estimates do not consider the proposed alternate flat dosing regimen of 360mg Q3W for nivolumab. Average patient weight may also be higher in the PBS setting, as a greater proportion of patients are likely to be male vs in the trial.
IPI	\$ ³ / infusion		

Abbreviations: 1L, first-line treatment; 2L, second-line treatment; DPMA, dispensed price at maximum amount; DUSC, Drug Utilisation Subcommittee; IPI, ipilimumab; MPM, malignant pleural mesothelioma; NIVO, nivolumab; PBAC, Pharmaceutical Benefits Advisory Committee; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks

Source: Tables 105,106,109,113 of the submission, with additional numbers from Excel model 'Nivolumab plus ipilimumab MPM Utilisation and Cost Model.xlsx'

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

³ 5,000 to < 10,000

6.66 A summary of the estimated use and financial impact of NIVO+IPI is presented in the table below.

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Table 20: Estimation of use and financial impact of the proposed medicine

	2022 ^A	2023	2024	2025	2026	2027
Estimation of number of treated patients						
1L MPM						
Incident mesothelioma population	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Total 1L patients treated with NIVO+ IPI	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
2L MPM (pts diagnosed 2020, 2021)						
Incident mesothelioma population	■ ¹	-	-	-	-	-
Total 2L patients treated with NIVO+ IPI	■ ²	-	-	-	-	-
Total patients treated with NIVO+ IPI (1L + 2L)	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Estimated effective cost of NIVO+ IPI to PBS/RPBS						
Net cost NIVO (1L +2L)	\$ ■ ³	\$ ■ ⁴	\$ ■ ³	\$ ■ ³	\$ ■ ³	\$ ■ ³
Net cost IPI (1L + 2L)	\$ ■ ⁴	\$ ■ ⁴	\$ ■ ⁴	\$ ■ ⁴	\$ ■ ⁴	\$ ■ ⁴
Net cost NIVO + IPI (1L +2L)	\$ ■ ³	\$ ■ ³	\$ ■ ³	\$ ■ ³	\$ ■ ³	\$ ■ ³
Estimation changes in use and financial impact of currently listed chemotherapy*						
Total number of patients who would have been treated with CHEMO displaced by PBS listing of NIVO + IPI (1L +2L)	■ ² (incl. ■ ² in 2L)	■ ²	■ ²	■ ²	■ ²	■ ²
Total cost offset to PBS/RPBS	-\$ ■ ⁵	-\$ ■ ⁵	-\$ ■ ⁵	-\$ ■ ⁵	-\$ ■ ⁵	-\$ ■ ⁵
Estimated financial implications for the PBS/RPBS and the health budget						
Net cost PBS/RPBS, proposed listing (net cost offsets)	\$ ■ ³	\$ ■ ³	\$ ■ ³	\$ ■ ³	\$ ■ ³	\$ ■ ³
Net cost to MBS	\$ ■ ⁴	\$ ■ ⁴	\$ ■ ⁴	\$ ■ ⁴	\$ ■ ⁴	\$ ■ ⁴
Net change to PBS/RPBS/ MBS	\$ ■ ³	\$ ■ ³	\$ ■ ³	\$ ■ ³	\$ ■ ³	\$ ■ ³

Notes: ^Anote 2L costs have only been assumed for 2022 year (accounting for patient who have started chemo while awaiting PBS listing of NIVO+IPI); *chemotherapy split: 100% pemetrexed, 33% cisplatin, 67% carboplatin

Abbreviations: Abbreviations: 1L, first-line treatment; 2L, second-line treatment; Chemo, pemetrexed plus cisplatin/carboplatin; incl. including; IPI, ipilimumab; NIVO, nivolumab

Source: Tables 106, 108, 110, 111,114, 115, 116, 117, 118 of submission and compiled during the evaluation

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

³ \$10 million to < \$20 million

⁴ \$0 to < \$10 million

⁵ net cost saving

6.67 The submission estimated the net cost to PBS/RPBS to be approximately \$80 million to < \$90 million (plus \$0 to < \$10 million net cost to MBS) over the first six years of listing.

6.68 The DUSC agreed with the PSCR that there is likely to be a small prevalent pool for use as a second line treatment in unresectable MPM however noted that there may also be a proportion of patients who relapse following surgery where 33% of patients have received adjuvant chemotherapy. The DUSC considered that the second line population may be larger than anticipated and leakage into the adjuvant and potentially neo-adjuvant setting may result in increased financial costs to the PBS. The pre-PBAC response included an additional < 500 patients per year to account for patients who have relapsed after surgery.

- 6.69 The DUSC noted that the Australian population accessing NIVO+IPI would be older and frailer than the population in the clinical trial and therefore the trial is likely to underestimate the number of patients treated with nivolumab monotherapy. The DUSC noted that there is also a risk of leakage into patients with an ECOG of ≥ 2 . A retrospective study done on patients presenting to a clinic in Australia from January 2012 to July 2018 for unresectable MPM found 21% of patients presented with an ECOG of ≥ 2 . The DUSC noted that this could result in this group of patients beginning treatment on NIVO+IPI and subsequently stepping down to the more tolerable nivolumab monotherapy, particularly in the context of recent research findings relating to the effectiveness of monotherapy in the second line setting.
- 6.70 The DUSC noted that mesothelioma can develop 20 to 60 years after exposure to asbestos and that Australia's ban on asbestos use occurred in December 2003. The DUSC noted that the incident rate of mesothelioma is likely to increase and the rate of 2.78 per 100,000 is an underestimate. The PBAC agreed with the DUSC that an incidence of 3.0 per 100,000 would be more appropriate.
- 6.71 The evaluation noted that the uptake rate is likely underestimated due to the substantial improvement in OS in the non-epithelioid subgroup of MPM which comprised 47.5% of the total MPM population in 2019 in Australia. The DUSC agreed with the evaluation that it is likely that a higher proportion of these patients would uptake NIVO+IPI. The DUSC noted a sensitivity analysis showed a 20% relative increase in uptake rate translated to 19.67% increase in total six year cost to the PBS from \$80 million to < \$90 million to \$100 million to < \$200 million. The PBAC considered the relative uptake in patients with non-epithelioid MPM may be higher than the 10% applied in the submission but also considered the relative uptake in patients with epithelioid MPM may be lower than 10%. Overall, the PBAC considered a 10% relative increase in uptake across the MPM population, which resulted in an uptake of NIVO + IPI of 58.99% was uncertain but a reasonable assumption.
- 6.72 The DUSC agreed with the evaluation that flat dosing is likely to increase financial costs to the PBS. The DUSC acknowledged the sponsor's willingness to work with the PBAC/Department of Health as outlined in the PSCR to enter a Risk Share Arrangement to offset the points of uncertainty and mitigate risk to the government. The pre-PBAC response states that while it is correct that, for some patients, use of weight based dosing would result in a higher cost per patient compared to flat dosing, this can be negated by the introduction of a restriction note in line with existing NIVO listings. This note would ensure that weight based dosing is used only in patients for whom the cost per infusion would be equal to or lesser than flat dosing (that is, patients 80kg or less).
- 6.73 The DUSC noted that the addition of < 500 patients on compassionate supply from the Sponsor to the financial estimates in the PSCR resulted in an increase of approximately \$0 to < \$10 million to the net cost to the PBS/RPBS in the first year of listing (assuming full treatment cost). The PBAC noted the number of patients was increased to < 500 in the pre-PBAC response and the cost per patient was reduced to account for treatment already received.

Financial Management – Risk Sharing Arrangements

- 6.74 The submission reported that the sponsor is willing to enter a risk-sharing agreement, including possible subsidisation caps. The submission stated that there is the potential for treatment to be received by other mesothelioma patients (e.g. peritoneal mesothelioma). The submission stated that the PBS restriction restricts access to immunotherapy retreatment and therefore mitigates risk of repeated administration with NIVO + IPI.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required (Streamlined) listing of nivolumab in combination with ipilimumab (NIVO+IPI), for the treatment of malignant pleural mesothelioma (MPM). The PBAC considered that there was a high clinical need for effective therapies for MPM, and NIVO+IPI is likely to provide a substantial clinical benefit compared to pemetrexed-based chemotherapy for some patients. The PBAC considered it would be appropriate for the listing of NIVO+IPI to allow use in the first- and second-line treatment setting and in the small number of patients with unresectable disease and non-pleural mesothelioma. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of NIVO+IPI could be brought into an acceptable range with a price reduction. The PBAC considered a risk share arrangement (RSA) would be required to manage the uncertainty associated with the number of patients that would be treated.
- 7.2 The PBAC is satisfied that nivolumab in combination with ipilimumab provides, for some patients, a significant improvement in efficacy over pemetrexed-based chemotherapy.
- 7.3 The PBAC noted there is a high clinical need for effective treatments for MPM and considered NIVO+ IPI provides a substantial net clinical benefit. The PBAC noted this was supported by the consumer comments received for this submission.
- 7.4 The PBAC noted the proposed TGA indication was for the first line treatment of unresectable MPM. The PBAC noted the submission requested a listing for unresectable MPM that did not specify line of treatment. The submission presented a number of naïve indirect comparisons of NIVO+IPI and BSC in the second- and later-line settings to support use in these treatment settings. The PBAC considered the comparison of NIVO+IPI and BSC was uninformative due to the heterogeneity observed in the trials.
- 7.5 The submission presented one head-to-head randomised, Phase III, open-label trial comparing NIVO+IPI to pemetrexed-based chemotherapy for the first-line treatment of unresectable MPM (CheckMate 743, n=605). The PBAC noted the median OS was 18.1 months in the NIVO+IPI treatment arm and 14.1 months in the pemetrexed-

based chemotherapy treatment arm with a HR for OS of 0.74 (95% CI: 0.60, 0.91). The PBAC noted there was no benefit for patients treated with NIVO+IPI for PFS, disease control rate or response rate, and the quality of life data was inconclusive due to small patient numbers. The PBAC noted that, as observed in other indications, there was an increased risk of early progression for patients receiving NIVO+IPI compared to pemetrexed-based chemotherapy.

- 7.6 The PBAC noted that the evidence of a benefit was weak in subgroup analyses for people with epithelioid histology, PD-L1 expression $\leq 1\%$ or aged older than 75 years. The CheckMate 743 study was not powered to exclude an OS benefit in subgroups and, on balance, the PBAC considered it was not reasonable to limit access to NIVO + IPI based on the subgroup analyses.
- 7.7 The PBAC considered NIVO+IPI was of inferior safety compared to pemetrexed-based chemotherapy but the AE profile was manageable. The PBAC noted a higher proportion of patients in the NIVO+IPI treatment arm experienced Grade 3 or 4 AEs compared to patients in the pemetrexed-based chemotherapy arm and a higher proportion discontinued due to Grade 3 or 4 AEs.
- 7.8 The PBAC noted the base case ICER presented in the submission was \$55,000 to < \$75,000 per QALY gained. The PBAC noted this was based on extrapolation of OS from 17.35 months in the NIVO +IPI arm and 13.27 months in the pemetrexed-based chemotherapy and considered this was not appropriate as it did not make full use of the available KM data. The PBAC noted the ICER based on extrapolation of OS from 29.7 months (median follow-up for OS) was \$75,000 to < \$95,000 per QALY gained. The PBAC noted this model predicted approximately 5% of NVIO+IPI patients would be alive at 10 years, which may not be reasonable for an unresectable MPM population. The PBAC noted assuming extrapolation from 29.7 months and convergence of OS between 5 and 10 years (as proposed in the pre-PBAC response) resulted in an ICER of \$95,000 to < \$115,000 per QALY gained. The PBAC considered it was appropriate for the OS curves to converge over a 10 year time horizon and this was a reasonable ICER for decision-making. The PBAC considered NIVO+IPI would be cost effective if the ICER was between \$80,000 and \$90,000.
- 7.9 The PBAC considered that it was appropriate for NIVO+IPI to be available in the second-line treatment setting, given the lack of effective treatment options and that the evidence in the first-line setting demonstrating superiority is likely to be at least partially applicable for later line use. The PBAC also considered it would not be appropriate to exclude access to patients with non-pleural mesothelioma. The PBAC noted non-pleural mesothelioma accounted for approximately 7% of mesothelioma cases and considered it was reasonable to assume that allowing access for these patients would increase the patient numbers by < 500 per year.
- 7.10 The PBAC noted the pre-PBAC response indicated < 500 patients would require grandfathering onto PBS-subsidised treatment and these patients were added to the financial estimates with ~75% of the treatment cost applied to account for treatment

already received. The PBAC considered it was appropriate to add the cost of treating the GF patients to the financial estimates and to assume only a proportion of their treatment cost will be PBS-subsidised.

- 7.11 The PBAC considered it was reasonable to apply an incidence of MPM of 3.0 per 100,000 patients to estimate the number of patients that would be eligible for NIVO+IPI. Additionally, the number of treated patients should be amended to include the GF patients (paragraph 7.10), patients with non-pleural mesothelioma (paragraph 7.9) and patients who have relapsed after surgery (paragraph 6.68).
- 7.12 The PBAC advised that a risk sharing arrangement with expenditure caps based on the cost of NIVO+IPI as defined by the patient numbers in paragraphs 7.11 would be required. The PBAC considered the number of second line patients who would access treatment, and the associated cost-effectiveness, as well as the impact of flat dosing on overall financial costs, to be uncertain. Acknowledging the high clinical need in patients with MPM and the limited risk of substantial use beyond the recommended patient population, the PBAC considered a rebate of less than ■■■% for use above the expenditure caps may be appropriate, however any rebate would need to require the sponsor to rebate the majority of the cost of use outside the defined RSA cap to ensure control of any non cost-effective use.
- 7.13 The PBAC advised the following changes to the restriction criteria were appropriate:
- A single restriction criteria (rather than initial and continuing criteria) as proposed by the Secretariat in paragraph 3.1;
 - Change the number of repeats to 8 for nivolumab and include an administration note: *“An increase of number of repeats may be authorised up to 11 if the patient is receiving a weight based dosing of 3mg/kg every 2 weeks”*.
 - Change the number of repeats to 3 for ipilimumab.
 - Inclusion of the clinical criteria: *“The treatment must not exceed a maximum of 24 months in a lifetime for this condition”*.
 - Removal of ‘pleural’.
- 7.14 The PBAC found that the criteria prescribed by the *National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for NIVO+IPI:
- (a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over the nominated comparator in terms of overall survival in the unresectable MPM patient population;
 - (b) The treatment is expected to address a high and urgent unmet clinical need as the current medicines available for the treatment of patients with unresectable MPM have limited efficacy;

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(c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
NIVOLUMAB Injection	NEW (Public) NEW (Private)	360mg	8	Bristol-Myers Squibb Australia Pty Ltd
Available brands				
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)				
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)				

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Medicare; retrospective audit of patient records possible)
Episodicity: [nil]
Severity: Unresectable
Condition: Malignant mesothelioma
Indication: Unresectable malignant mesothelioma
Clinical criteria:
Patient must have a WHO performance status of 0 or 1.
AND
The treatment must be in combination with PBS-subsidised ipilimumab, unless an intolerance to ipilimumab of a severity necessitating permanent treatment withdrawal of ipilimumab
AND
Patient must not have developed disease progression while being treated with this drug for this condition
AND
The treatment must not exceed a maximum total of 24 months in a lifetime for this condition.
Administrative Advice: No increase in the maximum number of repeats may be authorised
Administrative Advice: Special Pricing Arrangements apply
Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.
CAUTION: Combination treatment with ipilimumab and nivolumab is associated with an increased incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.
An increase of number of repeats may be authorised up to 11 if the patient is receiving a weight based dosing of 3mg/kg every 2 weeks.
The patient's body weight must be documented in the patient's medical records at the time treatment is initiated

Add new indication to ipilimumab as follows:

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Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Proprietary name and manufacturer
IPILIMUMAB 50 mg/10 mL injection, 10 mL vial	120 mg	3	Yervoy® Bristol-Myers Squibb Australia Pty Ltd

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Medicare; retrospective audit of patient records possible)
Episodicity: [nil]
Severity: Unresectable
Condition: Malignant mesothelioma
Indication: Unresectable malignant mesothelioma
Clinical criteria:
Patient must have a WHO performance status of 0 or 1.
AND
The treatment must be in combination with PBS-subsidised nivolumab for this condition
AND
Patient must not have developed disease progression while being treated with this drug for this condition
AND
The treatment must not exceed a maximum total of 24 months in a lifetime for this condition.
Administrative Advice: No increase in the maximum number of repeats may be authorised
Administrative Advice: Special Pricing Arrangements apply
Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.
CAUTION: Combination treatment with ipilimumab and nivolumab is associated with an increased incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.
No increase in the maximum number of repeats may be authorised.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The Sponsor welcomes the PBAC recommendation to list nivolumab plus ipilimumab for the treatment of unresectable malignant mesothelioma. The Committee's pragmatic decision to grant a broad PBS restriction that includes use in the first-line and second-line treatment setting and in the small number of patients with non-pleural mesothelioma provides important access to a group of patients with high unmet clinical need. The Sponsor acknowledges the collective effort from multiple stakeholders to achieve this outcome and looks forward to partnering with the Department to achieve PBS listing as soon as practicable.