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 Section 100 listing for nivolumab plus ipilimumab in combination with two cycles of platinum-based doublet chemotherapy (herein referred to as NIVO+IPI+platinum) for the treatment of previously untreated Stage IV non-small cell lung cancer (NSCLC) in patients who do not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour tissue (i.e. EGFR and ALK negative).

1.2 Listing was requested on the basis of a cost-minimisation analysis versus pembrolizumab plus platinum-based doublet chemotherapy (herein referred to as pembrolizumab+platinum).

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

Component	Description
Population	Patients with metastatic (Stage IV) non-small cell lung cancer (NSCLC) who have not previously been treated in the metastatic setting.[a]
Intervention	Nivolumab plus ipilimumab and two cycles of platinum-based doublet chemotherapy
Comparator	Pembrolizumab plus platinum-based doublet chemotherapy (primary comparator) Atezolizumab plus bevacizumab and platinum-based doublet chemotherapy Platinum-based doublet chemotherapy Pembrolizumab monotherapy Nivolumab plus ipilimumab (near market comparator)
Outcomes	Overall survival, rate and nature of adverse events.
Clinical claim	Non-inferior in terms of efficacy with a different and non-inferior safety profile compared with pembrolizumab plus platinum-based chemotherapy. Non-inferior in terms of efficacy with a different and non-inferior safety profile compared with atezolizumab plus bevacizumab and platinum-based chemotherapy. Superior in terms of efficacy with an inferior but acceptable safety profile compared with platinum-based chemotherapy. Non-inferior in terms of efficacy with an inferior but acceptable safety profile compared with pembrolizumab monotherapy.

Source: Table 1, p18 of the submission.

[a] The requested listing excludes patients with evidence of an activating epidermal growth factor (EGFR) gene or anaplastic lymphoma kinase (ALK) gene rearrangement in tumour tissue.

2 Background

Registration status

2.1 Nivolumab and ipilimumab were TGA registered on the 13 July 2020 for the following indications:

- Nivolumab, in combination with ipilimumab and 2 cycles of platinum-based chemotherapy, is indicated for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations.
- Ipilimumab, in combination with nivolumab and 2 cycles of platinum-based chemotherapy, is indicated for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations.

2.2 The PBAC noted NIVO+IPI (without chemotherapy) was not TGA registered as a first-line treatment for metastatic NSCLC at the time of consideration.

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 and form	Max Amt	№.of Rpts	Dispensed Price Max Amt	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 $7,561.36 public hospital $7,705.78 private hospital Effective price $[redacted] [a] public hospital $[redacted] [a] private hospital	Opdivo®	Bristol-Myers Squibb Australia Pty Ltd
IPILIMUMAB 50 mg/10 mL injection, 10 mL vial	120 mg	4 (initial and continuing treatment)	Published price $16,962.82 public hospital $17,238.86 private hospital Effective price $[redacted] [a] public hospital $[redacted] [a] private hospital	Yervoy®	Bristol-Myers Squibb Australia Pty Ltd

Category/Program:	Section 100 – Efficient funding of Chemotherapy (Public and Private Hospital)
PBS indication:	Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase:	Initial *combination treatment (with nivolumab/ ipilimumab and platinum based chemotherapy) as first-line drug therapy*
Restriction:	Streamlined
~~Treatment criteria:~~	~~Patient must be undergoing combination treatment with nivolumab/ipilimumab.~~
Clinical criteria:	Patient must not have previously been treated for this condition in the metastatic setting, AND 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 non-small cell lung cancer, AND Patient must have a WHO performance status of 0 or 1, AND The condition must ~~not~~ have evidence ~~of~~ *that* an activating epidermal growth factor (EGFR) gene *rearrangement and* ~~or~~ an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material. *AND* *The treatment must be in combination with nivolumab/ ipilimumab and platinum-based chemotherapy*
Treatment phase:	Continuing treatment
Restriction:	Streamlined
~~Treatment criteria:~~	~~Patient must be undergoing combination treatment with nivolumab/ipilimumab.~~
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug in this line of treatment, AND ~~Patient must have stable or responding disease,~~ *Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition* AND *The treatment must be in combination with nivolumab/ ipilimumab* Nivolumab/ ipilimumab: The treatment must not exceed ~~a total of 53 cycles or up to~~ 24 months *in total, measured from the initial dose, or, must not extend beyond disease progression, whichever comes first* ~~under this restriction.~~
Treatment phase:	Grandfathering treatment
Restriction:	Streamlined
Treatment criteria:	Patient must be undergoing combination treatment with nivolumab/ipilimumab.

Clinical criteria:	Patient must have received *non-PBS subsidised* treatment with this drug *as first-line drug therapy* for this *PBS indication* ~~condition~~ prior to [PBS listing date], AND ~~Patients must have stable or responding disease~~, *Patient must not have developed disease progression while receiving treatment with this drug for this condition* AND Patient must have a WHO performance status of 0 or 1 *prior to initiation of non-PBS subsidised treatment with this drug for this condition* *AND* *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 non-small cell lung cancer,* AND *The condition must have evidence that an activating epidermal growth factor (EGFR) gene rearrangement and an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material* AND ~~The treatment must not exceed a total of 18 cycles or up to 24 months under this restriction~~. Nivolumab/ ipilimumab: The treatment must not exceed ~~a total of 53 cycles or up to~~ 24 months *in total, measured from the initial dose, or, must not extend beyond disease progression, whichever comes first* ~~under this restriction~~

[a] The effective prices were derived in the cost-minimisation analysis based on an assumed 30% rebate for pembrolizumab and are only a placeholder.

3.2 The sponsor acknowledged that there is a special pricing arrangement (SPA) in place for pembrolizumab. The effective prices for nivolumab and ipilimumab above are based on an assumed 30% SPA rebate for pembrolizumab, and the sponsor has indicated that they will revise the effective price based on a cost minimisation against the actual effective price of pembrolizumab upon recommendation.

3.3 The submission proposed that the effective price for nivolumab in the first-line Stage IV NSCLC setting be equivalent to the effective price in the second-line setting for NSCLC ($[redacted]/100 mg vial). The effective price for ipilimumab was subsequently derived in the cost-minimisation analysis. Ipilimumab is not currently listed on the PBS for the treatment of NSCLC.

3.4 The requested restrictions for nivolumab and ipilimumab were broader than the approved TGA indications, in that they do not state that nivolumab plus ipilimumab should be initiated in combination with two cycles of platinum-based doublet chemotherapy.

3.5 The Pre-Sub-Committee Response (PSCR) argued that it was reasonable for the proposed PBS restrictions to omit that treatment must be in combination with two cycles of platinum-based chemotherapy, given chemotherapy is a general schedule item and is only included in the first two cycles of the dosing regimen. The PSCR further stated that the proposed restriction was appropriate, as it is consistent with the PBS restrictions for pembrolizumab plus chemotherapy for metastatic NSCLC, which do not specify that pembrolizumab should be initiated with four cycles of platinum-based doublet chemotherapy. The ESC noted treatment with nivolumab + ipilimumab (without concurrent platinum-doublet chemotherapy) is not TGA registered and [redacted]

[redacted] The ESC considered the requirement for concurrent use of platinum-based doublet chemotherapy should be included in the initial PBS restriction until such time the PBAC had recommended initial treatment nivolumab + ipilimumab without chemotherapy.

3.6 The PBAC advised the restrictions for initial treatment for both nivolumab and ipilimumab should preclude their use in patients who have evidence of a c-ROS proto-oncogene-1 (ROS1) gene rearrangement in tumour material.

3.7 The submission estimated that approximately <500 patients from the patient familiarisation program would transfer to PBS-subsidised treatment if nivolumab and ipilimumab are listed as requested.

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

4 Population and disease

4.1 Lung cancer is the fifth most commonly diagnosed cancer in Australia, with NSCLC representing an estimated 86.6% of all incident lung cancer in Australia. It was estimated that there will be approximately 11,250 incident cases of NSCLC in Australia in 2020. NSCLC can have squamous or non-squamous histology, with the choice of chemotherapy differing between the two types. Approximately 50% of patients with NSCLC are diagnosed with Stage IV (metastatic disease). Survival data for NSCLC patients diagnosed with distant (metastatic) disease, from the Surveillance, Epidemiology, and End Results program in the United States, reported a 5-year survival rate of only 4.7% in 2019; Australian-specific five year survival of Stage IV NSCLC was not available.

4.2 The PBAC has previously considered several treatments in first-line stage IV NSCLC, including pembrolizumab plus platinum-based doublet chemotherapy, the nominated primary comparator.

4.3 It was proposed that:

- In patients with previously untreated Stage IV non-squamous or not otherwise specific (NOS) NSCLC without targetable mutations (i.e. EGFR, ALK and ROS1 negative), NIVO+IPI+platinum would be an alternative to pembrolizumab+platinum, atezolizumab plus bevacizumab plus platinum-based doublet chemotherapy (herein referred to as atezolizumab+bevacizumab+platinum), pembrolizumab monotherapy and platinum-based doublet chemotherapy; and

- In patients with previously untreated Stage IV squamous NSCLC, NIVO+IPI+platinum would be an alternative to pembrolizumab+platinum, pembrolizumab monotherapy and platinum-based doublet chemotherapy.

The requested listings for nivolumab and ipilimumab restrict their use to patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1.

4.4 The proposed intervention is a combination of nivolumab and ipilimumab, initiated in combination with two cycles of platinum-based doublet chemotherapy. Under the requested restrictions, both nivolumab and ipilimumab can be continued for up to 24 months. The requested initial treatment and continuing treatment restrictions for both drugs stipulate that patients must be undergoing combination treatment with nivolumab and ipilimumab. This is consistent with the TGA-approved Product Information (PI) documents, which state that, when nivolumab and ipilimumab are administered in combination, if either agent is withheld, the other agent should also be withheld.

4.5 Nivolumab (ATC code L01XC17) is a fully human immunoglobulin G4 (IgG4) monoclonal antibody which binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2. Ipilimumab (ATC code L01XC11) is a fully human monoclonal antibody which binds to the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Nivolumab potentiates T-cell anti-tumour responses whereas ipilimumab blocks T-cell inhibitory signals, with the two drugs working synergistically via different mechanisms of actions to increase immune response against tumours.

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

5 Comparator

5.1 The submission nominated pembrolizumab plus platinum-based doublet chemotherapy (pembrolizumab+platinum) as the primary comparator. The main arguments provided in support of this nomination were that pembrolizumab plus platinum-based doublet chemotherapy is PBS listed as first-line therapy in stage IV NSCLC and was suggested by clinicians to be the immunotherapy based regimen most likely replaced. The ESC considered pembrolizumab+platinum is an appropriate comparator. In contrast to NIVO+IPI+platinum, in which only two cycles of chemotherapy are administered, pembrolizumab+platinum is initiated with four cycles of platinum-doublet chemotherapy.

5.2 The submission also nominated atezolizumab plus bevacizumab plus platinum-based doublet chemotherapy (in patients with non-squamous NSCLC only) and platinum-based doublet chemotherapy alone as secondary comparators, and pembrolizumab monotherapy as a supplementary comparator (in patients with programmed cell death ligand-1 (PD-L1) tumour proportion score (TPS) ≥1%). While international treatment guidelines recommend pembrolizumab monotherapy as a first-line treatment for patients with advanced or metastatic NSCLC expressing PD-L1 (TPS

≥50%)[*], the extent of substitution of NIVO+IPI+platinum for pembrolizumab monotherapy is likely to be limited due to the potential additional toxicity associated with ipilimumab and platinum-doublet chemotherapy. The clinical decision making criteria that would result in the preference of pembrolizumab monotherapy over pembrolizumab+platinum would likely be the same that would preference pembrolizumab monotherapy over NIVO+IPI+platinum. Given this, the comparison of NIVO+IPI+platinum versus pembrolizumab monotherapy is not presented in Section 6.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from three organisations via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with NIVO+IPI+platinum including fewer side effects related to reduced cycles of chemotherapy. The Lung Foundation of Australia also commented on the importance to consumers of having additional treatment options for patients with NSCLC, even if there was no difference in clinical outcomes.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the NIVO+IPI+platinum submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for NIVO+IPI+platinum, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement), based on a comparison with platinum-based chemotherapy[†].

Clinical trials

6.4 The comparison of NIVO+IPI+platinum versus pembrolizumab+platinum and atezolizumab+bevacizumab+platinum was based on indirect comparisons using the following six trials:

- CheckMate 9LA (CM9LA): a randomised, open-label trial of NIVO+IPI+platinum (N=361) versus platinum-doublet chemotherapy (N=358) in patients with

[*] Planchard D, Popat S*, et al.* Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018; 29 (Suppl 4):iv192-iv237 and National Comprehensive Cancer Network. *Non-small cell lung cancer.* NCCN Clinical Practice Guidelines in Oncology [Internet]. 2020. [Accessed 21 July 2020]]; Version 5.2020. Available from: https://www.nccn.org/.

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

previously untreated metastatic NSCLC, irrespective of histology or PD-L1 expression status;

- Keynote 189 (KN189): a randomised, double-blind trial comparing pembrolizumab+platinum (N=410) with placebo+platinum (N=206) in patients with previously untreated metastatic non-squamous NSCLC, irrespective of PD-L1 expression status;
- Keynote 407 (KN407): a randomised, double-blind trial comparing pembrolizumab+platinum (N=278) with placebo+platinum (N=281) in patients with previously untreated metastatic squamous NSCLC, irrespective of PD-L1 expression status;
- IMpower150: a randomised, open-label trial comparing atezolizumab+bevacizumab+platinum (N=402) with atezolizumab+platinum (N=400) and bevacizumab+platinum (N=400) in patients with previously untreated metastatic non-squamous NSCLC, irrespective of PD-L1 expression status;

6.5 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 9LA	Interim analysis Clinical Study Report: A Phase 3, randomized study of nivolumab plus ipilimumab in combination with chemotherapy vs chemotherapy alone as first line therapy in Stage IV non-small cell lung cancer (NSCLC). Updated analysis Clinical Study Report: A Phase 3, randomized study of nivolumab plus ipilimumab in combination with chemotherapy vs chemotherapy alone as first line therapy in Stage IV non-small cell lung cancer (NSCLC).	January 2020 June 2020
Keynote 189 (KN 189)	Gandhi L, Rodriguez-Abreu D, Gadgeel S et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. Gadgeel S, Rodriguez-Abreau D Speranza G et al. Updated analysis from Keynote-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer.	*NEJM* 2018; 378: 2078-2092. *Journal of Clinical Oncology* 2020; 38: 1505-1517.
Keynote 407 (KN 407)	Paz-Ares L. Luft A, Vicente D et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. Paz-Ares L, Vicente D, Tafreshi A et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous non-small-cell lung cancer: protocol-specified final analysis of Keynote-407. Paz-Ares L, Vicente D, Tafreshi A et al. Pembrolizumab plus chemotherapy in metastatic squamous NSCLC: final analysis and progression after the next line of therapy (PFS2) in Keynote-470. Halmos B, Luft A, Majem M et al. Choice of taxane and outcomes in the Keynote-407 study of pembrolizumab plus chemotherapy for metastatic squamous NSCLC.	*NEJM* 2018; 379: 2040-2051. *Journal of Thoracic Oncology* 2020, doi: 10.1016/jtho.2020.06.015 [Epub ahead of print]. *Annals of Oncology* 2019; 30(suppl 5): pp.mdz 394-080. *Journal of Thoracic Oncology* 2018; 13(10 supplement): S391.
IMpower 150	Socinski M, Jotte R, Cappuzzo F et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. Reck M, Wehler T, Orlandi F et al. Safety and patient-reported outcomes of atezolizumab plus chemotherapy with or without bevacizumab versus bevacizumab plus chemotherapy in non-small-cell lung cancer. Socinski M, Mok S, Nishio M et al. IMpower150 final analysis: Efficacy of atezolizumab and chemotherapy ± bevacizumab in first-line metastatic non-squamous non-small cell lung cancer across key subgroups.	*NEJM* 2018; 378: 2288-2301. *Journal of Clinical Oncology* 2020; 38(22): 2530-2542. American Association for Cancer Research Virtual Annual Meeting 2020 June 22-24.

Source: Table 23 p64, Table 24 pp65-67 and Table 25 pp68-69 of the submission; Attachment 1 to the submission.

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

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome
NIVO+IPI+platinum vs. platinum chemotherapy					
CM9LA	719	R, OL 14.2/10.9 mths[a]	Low[b]	Untreated Stage IV NSCLC, EGFR and ALK mutation negative, ECOG PS 0 or 1	OS
pembrolizumab+platinum vs. placebo+platinum chemotherapy					
KN189	616	R, DB 23.1 mths	Low	Untreated Stage IV non-squamous NSCLC, EGFR and ALK mutation negative, ECOG PS 0 or 1	OS
KN407	559	R, DB 7.8/14.3 mths[c]	Low	Untreated Stage IV squamous NSCLC, EGFR and ALK mutation negative, ECOG PS 0 or 1	OS
Atezolizumab+bevacizumab+platinum vs. bevacizumab+platinum chemotherapy					
IMpower150	1202[d]	R, OL 15.4/20/39.3 mths[e]	Low[b]	Untreated non-squamous Stage IV NSCLC, ECOG PS 0 or 1	OS

Source: Table 28 pp77-79; Table 29 p 83, Table 30 pp85-91; Table 51 p115, Table 52 p116, Table 53 p116, Table 54 p117 of the submission; p6 CM9LA Updated Analysis CSR; Socinski et al (2018); Socinski et al (2020); Mok et al (2019).

ALK = anaplastic lymphoma kinase; DB = double blind; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; OL = open label; OS = overall survival; R = randomised.

[a] Median follow-up in the NIVO+IPI+platinum and platinum chemotherapy arms, respectively. Source: p6 CM9LA Updated Analysis CSR.

[b] Low risk of bias for OS, high risk of bias for subjective outcomes.

[c] The clinical evidence for pembrolizumab+platinum in patients with squamous NSCLC was based on the May 2019 data cut-off (median follow-up 14.3 months) while the duration of treatment used in the cost-minimisation analysis presented in the submission was based on the April 2018 data cut-off (median follow-up 7.8 months)

[d] Only the WT-ITT population (wild type ITT population, i.e. EGFR and ALK mutation negative) in the atezolizumab+bevacizumab+platinum arm are relevant to the current submission (n=359).

[e] The duration of treatment was only reported for the September 2017 data cut-off (median follow-up 15.4 months in the WT-ITT population in the atezolizumab+bevacizumab+platinum arm). Analyses of OS outcomes were only available for the January 2018 data cut-off (median 20 months follow-up in the WT-ITT population in the atezolizumab+bevacizumab+platinum arm) and the September 2019 data cut-off (minimum follow-up 39.3 months across the atezolizumab+bevacizumab+platinum and the bevacizumab+platinum arms).

6.7 While CM9LA and IMpower150 were open-label studies, the risk of bias for the outcome of overall survival (OS), which is an objective outcome, was considered to be low.

Comparative effectiveness

6.8 The results for OS in CM9LA are presented in Table 4 and the Kaplan-Meier curve for OS is presented in Figure 1.

Table 4: OS outcomes in CM9LA, by clinical cut-of date (ITT analysis)

Clinical cut-off date	August 2019		February 2020	
	NIVO+IPI+platinum	Platinum chemo	NIVO+IPI+platinum	Platinum chemo
Median follow-up	10.4 months[a]	9.1 months[a]	14.2 months[b]	10.9 months[b]
ITT	N=361	N=358	N=361	N=358
Patients with event, n (%)	156 (43.2%)	195 (54.5%)	190 (52.6%)	242 (67.6%)
Median OS (95%CI), months	14.1 (13.2, 16.2)	10.7 (9.5, 12.5)	15.6 (13.9, 20.0)	10.9 (9.5, 12.6)
HR (95%CI)	0.69 (0.56, 0,86)		0.66 (0.55, 0.80)	
12-month OS rate	NA	NA	62.9%	46.9%

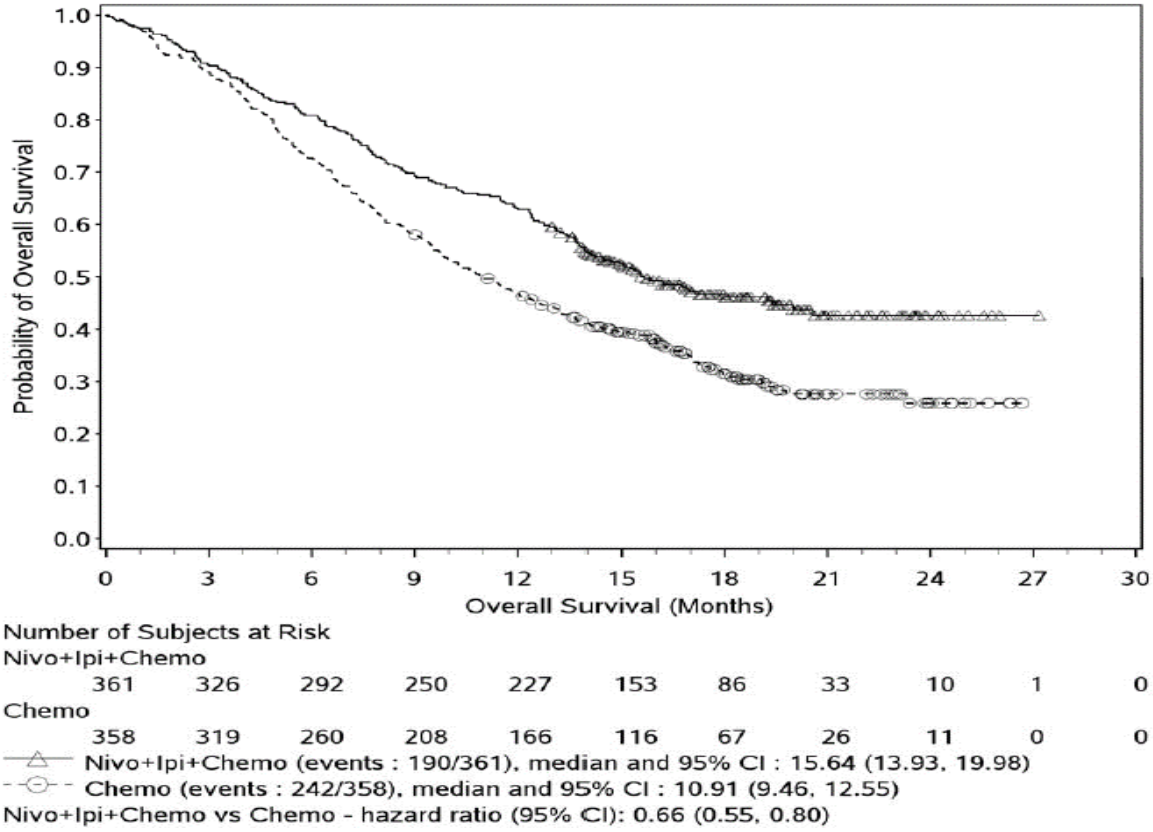
Source: Table 61 p131 and Table 63 p134 of the submission; Table 5, p10, Table 7.5-1 p98 and Figure 7.5-1, p99 CheckMate 9LA Interim Analysis CSR; Table 4, p 9, Table 6.5-1 p95 and Figure 6.5-1 p97 CheckMate 9LA updated Analysis CSR

Chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; NA = not available; OS = overall survival

[a] Minimum follow-up 8.1 months for OS

[b] Minimum follow-up 12.7 months for OS

Figure 1: Kaplan-Meier plot of OS – NIVO+IPI+platinum vs platinum chemotherapy (ITT, all histology)



Source: Figure 15, p133 of the submission; Figure 6.2-1, p73 CM9LA updated analysis CSR (February 2020 clinical cut-off).
Chemo = platinum-doublet chemotherapy; CI = confidence interval; Ipi = ipilimumab; ITT = intention to treat; Nivo = nivolumab; OS = overall survival.

6.9 The submission claimed that NIVO+IPI+platinum is superior to platinum-doublet chemotherapy in terms of OS, and that the improvement in OS was clinically meaningful. This ESC considered this was reasonable.

6.10 The OS results for pembrolizumab+platinum versus placebo+platinum from KN189 (non-squamous NSCLC) and KN407 (squamous NSCLC) are presented below.

Table 5: OS outcomes in KN189 and KN407

Keynote 189 – non-squamous NSCLC				
Clinical cut-off	**November 2017**		**September 2018**	
	PEMBRO+platinum	**Placebo+platinum**	**PEMBRO+platinum**	**Placebo+platinum**
Median follow-up	10.5 months		23.1 months	
ITT	N=410	N=206	N=410	N=206
Patients with event, n (%)	NR	NR	213 (52.0%)	144 (69.9%)
Median OS (95%CI), months	NR	11.3 (8.7, 15.1)	22.0 (19.5, 25.2)	10.7 (8.7, 13.6)
HR (95%CI)	0.49 (0.38, 0.64)		0.56 (0.45, 0.70)	
12-month OS rate	69.2%	49.4%	70.0%	48.1%
Keynote 407 – squamous NSCLC				
Clinical cut-off	**April 2018**		**May 2019**	
	PEMBRO+platinum	**Placebo+ platinum**	**PEMBRO+platinum**	**Placebo+ platinum**
Median follow-up	7.8 months		14.3 months	
ITT	N=278	N=281	N=278	N=281
Patients with event, n (%)	NR	NR	168 (60.4%)	197 (70.1%)
Median OS (95%CI), months	15.9 (13.2, NR)	11.3 (9.5, 14.8)	17.1 (14.4, 19.9)	11.6 (10.1, 13.7)
HR (95%CI)	0.64 (0.49, 0.85)		0.71 (0.58, 0.88)	
12-month OS rate	65.2%	48.3%	64.7%	49.6%

Source: Table 70 p145, Table 77 p154, and Figure 21 p146 of the submission; Paz-Ares et al (2020)
CI = confidence interval; HR = hazard ratio; ITT = intention to treat; NE = not evaluable; NR = not reported; NSCLC = non-small cell lung cancer; OS = overall survival; PEMBRO = pembrolizumab.
Note: the data for KN189 were previously considered by the PBAC in recommending pembrolizumab+platinum for listing for this indication (Pembrolizumab Public Summary Document (PSD), July 2019 PBAC meeting); the data for KN407 were considered in Agenda item 11.05, Broad PBS subsidy listing for PD-(L)1 checkpoint inhibitors for NSCLC, August 2019 PBAC meeting.

6.11 The indirect comparisons presented in the submission are summarised in Table 6.

Table 6: Summary of comparative evidence presented in the submission

Comparator	**Non-squamous NSCLC**	**Squamous NSCLC**
Pembrolizumab+platinum (Primary comparator)	Adjusted indirect comparison of HR for OS: CM9LA subgroup with NSQ NSCLC, versus KN189 ITT population (NSQ NSCLC).	Adjusted indirect comparison of HR for OS: CM9LA subgroup with SQ NSCLC, versus KN407 ITT population (SQ NSCLC).
Atezolizumab + bevacizumab + platinum (Secondary comparator)	Naïve indirect comparison of median OS: CM9LA subgroup with NSQ NSCLC versus IMpower150 ITT-WT population (NSQ NSCLC)[a]	NA

Source: compiled during the evaluation.
HR = hazard ratio; ITT = intention to treat; ITT-WT = intention to treat- wild type; NA = not applicable; NSCLC = non-small cell lung cancer; NSQ = non-squamous; OS = overall survival; PD-L1 = programmed cell death ligand 1; platinum = platinum-based doublet chemotherapy; SQ = squamous
[a] An adjusted indirect comparison of the HR for OS was not conducted due to the lack of a common comparator.

6.12 The submission proposed using the American Society of Clinical Oncology (ASCO) definitions for meaningful OS goals to inform a minimum clinically important difference (MCID) and also a non-inferiority criteria. ASCO suggested that a clinically meaningful improvement in OS for non-squamous NSCLC would be an improvement of 3.25-4.0 months and a target HR of 0.76-0.8, and for squamous NSCLC would be an improvement of 2.5-3 months with a target HR of 0.77-0.8. Based on these definitions, for the adjusted indirect treatment comparisons (ITCs) the proposed non-inferiority rules proposed in the submission were:

- In non-squamous patients: If the OS hazard ratio reported for the adjusted ITC of NIVO+IPI+platinum in the intention to treat (ITT) population of CM9LA versus pembrolizumab+ platinum in KN189 is <1.32 (inverse of 0.76) then non-inferiority is inferred.
- In squamous patients: If the OS hazard ratio reported for the adjusted ITC of NIVO+IPI+platinum in the ITT population of CM9LA versus pembrolizumab+ platinum in KN407 is <1.30 (inverse of 0.77) then non-inferiority is inferred.

For the unadjusted ITC of NIVO+IPI+platinum versus atezolizumab+bevacizumab+ platinum, the proposed non-inferiority rule was:

- If the difference in median OS for NIVO+IPI+platinum in the ITT population of CM9LA is ± 4.0 months the median OS reported for atezolizumab +bevacizumab +platinum in patients enrolled in the ITT wild type (ITT-WT) population IMpower150 then non-inferiority is inferred.

6.13 The proposed non-inferiority margins should have been applied to the upper 95% CI for HR for the OS in the comparison between NIVO+IPI+platinum with the nominated comparator (i.e. treatment with NIVO+IPI+platinum is no more than 32% (for non-squamous) or 30% (for squamous) worse than the comparator with regards to risk of death at the upper 95% confidence interval) to conclude non-inferiority.

NIVO+IPI+platinum versus pembrolizumab+platinum

6.14 The submission presented two adjusted indirect comparisons, CM9LA versus KN189 (non-squamous NSCLC) and CM9LA versus KN407 (squamous NSCLC), based on the HR for OS in each of the trials. The ITT population from CM9LA was used in the primary analysis for both comparisons, with a supplementary analysis based on the appropriate histological subgroup from CM9LA.

6.15 The submission noted that a higher proportion of patients in KN189 had an ECOG PS of 0 (44%) compared with the non-squamous subgroup in CM9LA (32%), and that this may potentially confound the indirect comparison in favour of pembrolizumab+platinum. The evaluation considered this was reasonable.

6.16 Approximately 40% of patients in KN407 received nab-paclitaxel as a component of platinum chemotherapy, while all patients with squamous NSCLC in CM9LA were treated with paclitaxel only. Nab-paclitaxel is not currently PBS listed for NSCLC; however, the ESC considered an indirect comparison only using the subgroup of patients in KN407 treated with paclitaxel was unlikely to be informative.

6.17 The submission also noted that a greater proportion of patients in KN189 and KN407 received subsequent immunotherapy compared with CM9LA. Of patients in the platinum chemotherapy arms of the trials, 30% in CM9LA, 54% in KN189 and 49% in KN407 received later-line immunotherapy. The use of immunotherapy following progression on first-line platinum chemotherapy is consistent with what would be expected in clinical practice in the scenario in which first-line immunotherapy is not available. The greater use of later-line immunotherapy in the control arm of the

pembrolizumab+platinum trials compared with the control arm in CM9LA is likely to have favoured NIVO+IPI+platinum over pembrolizumab+platinum in the indirect comparisons.

6.18 Differences in the duration of follow-up across the trials, and the consequent extent of use of later line immunotherapy in the comparator arms, have considerable potential to confound the indirect comparison, especially in the indirect comparison of patients with non-squamous NSCLC, who represent approximately 78% of the metastatic NSCLC population. This is illustrated by a sensitivity analysis, performed during the evaluation, using the OS results from the November 2017 data cut-off for KN189 (median follow-up 10.5 months) rather than the September 2018 data cut-off (median follow-up 23.1 months), as used in the submission (see Table 7). The indirectly derived HR for OS in the non-squamous NSCLC population increased from 1.23 (95% CI: 0.90, 1.69) based on the September 2018 data to 1.41 (95% CI: 1.00, 1.99) based on the November 2017 data from KN189 (see Table 7).

6.19 The PSCR presented an additional analysis based on a fractional polynomial-based network meta-analysis commissioned by the Sponsor after the PBAC deadline and used to support reimbursement applications in other jurisdictions. The PSCR argued that this exploratory assessment provided evidence that differences in trial follow-up of CM9LA and Keynote 189 do not impact the overall claim of non-inferiority made in the submission. The ESC noted the analysis was based on extrapolated OS data for each trial, that no information was provided regarding methodology and the analysis had not been evaluated.

6.20 The median OS in the common comparator arm of CM9LA (platinum-based doublet chemotherapy) for patients with non-squamous and squamous NSCLC (11.9 months and 9.1 months, respectively) was reasonably similar to median OS in the placebo+platinum arms of the corresponding pembrolizumab+platinum trials (10.7 months in KN189 and 11.6 months in KN407).

6.21 The results of the indirect comparison of OS for NIVO+IPI+platinum versus pembrolizumab+platinum in patients with non-squamous metastatic NSCLC are presented in Table 7.

Table 7: Adjusted indirect comparison of OS NIVO+IPI+platinum vs pembrolizumab+platinum, non-squamous NSCLC

	CheckMate 9LA		Keynote 189	
	NIVO+IPI+platinum	**Platinum chemo**	**PEMBRO+platinum**	**Placebo+platinum**
Primary analysis: ITT analysis				
Median follow-up	14.2 months	10.9 months	23.1 months[c]	
Population	All histology		Non-squamous	
	N=361	N=358	N=410	N=206
Patients with event, n (%)	190 (52.6%)	242 (67.6%)	213 (52.0%)	144 (69.9%)
Median OS (95%CI), months	15.6 (13.9, 20.0)	10.9 (9.5, 12.6)	22.0 (19.5, 25.2)	10.7 (8.7, 13.6)
HR (95%CI)	0.66 (0.55, 0.80)		0.56 (0.45, 0.70)	
12-month OS rate	62.9%	46.9%	70.0%	48.1%
Indirect estimate of effect, HR (95% CI)[a]			**1.18 (0.88, 1.58)**	
Supplementary analysis: non-squamous subgroup CM9LA				
Median follow-up	14.2 months[b]	10.9 months[b]	23.1 months[c]	
Population	Non-squamous subgroup		Non-squamous	
	N=246	N=246	N=410	N=206
Patients with event, n (%)	124 (50.4%)	159 (64.6%)	213 (52.0%)	144 (69.9%)
Median OS (95%CI), months	17.0 (14.0, NE)	11.9 (9.9, 14.1)	22.0 (19.5, 25.2)	10.7 (8.7, 13.6)
HR (95%CI)	0.69 (0.55, 0.87)		0.56 (0.45, 0.70)	
12-month OS rate	62.6%	50.0%	70.0%	48.1%
Indirect estimate of effect, HR (95% CI)[a]			**1.23 (0.90, 1.69)**	
Sensitivity analysis (non-squamous subgroup CM9LA) – KN189 November 2017 data cut-off				
Median follow-up	14.2 months[b]	10.9 months[b]	10.5 months[d]	
Population	Non-squamous subgroup		Non-squamous	
	N=246	N=246	N=410	N=206
Patients with event, n (%)	124 (50.4%)	159 (64.6%)	NR	NR
Median OS (95%CI), months	17.0 (14.0, NE)	11.9 (9.9, 14.1)	NR	11.3 (8.7, 15.1)
HR (95%CI)	0.69 (0.55, 0.87)		0.49 (0.38, 0.64)	
12-month OS rate	62.6%	50.0%	69.2%	49.4%
Indirect estimate of effect, HR (95% CI)[a]			***1.41 (1.00, 1.99)***	

Source: Table 76, p152 of the submission; Gandhi et al (2018). *Italicised values were calculated during the evaluation*
CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; ITC = indirect treatment comparison; ITT = intention to treat; NE = not evaluable; NIVO= nivolumab; OS = overall survival; PEMBRO = pembrolizumab
[a] Adjusted for the common reference.
[b] Median follow-up in ITT population.
[c] September 2018 data-cut-off
[d] November 2017 data cut-off

6.22 The submission stated that the indirectly derived HRs for OS for the primary analysis (CM9LA ITT: HR 1.18) and the supplementary analysis (non-squamous subgroup CM9LA: HR 1.23) were both less than the proposed non-inferiority margin of 1.32 for non-squamous NSCLC. On this basis, the submission claimed that, in patients with non-squamous NSCLC, NIVO+IPI+platinum is non-inferior to pembrolizumab+platinum for the patient relevant outcome of OS. This interpretation of the results of the indirect comparison is incorrect, as it is not appropriate to base the interpretation on the point estimate of the HR. The upper bound of the 95% CI for the indirectly derived HR for OS was 1.58 in the primary analysis and 1.69 in the supplementary analysis. The ESC agreed with the evaluation that as the upper limit of

the 95% CI in both analyses exceeded the non-inferiority margin, the indirect comparison failed to exclude the possibility that NIVO+IPI+platinum is clinically meaningfully inferior to pembrolizumab+platinum in terms of OS in this patient population. The ESC noted that the indirectly derived HR for OS in the non-squamous NSCLC population was 1.23 (95% CI: 0.90, 1.69) based on the September 2018 data and 1.41 (95% CI: 1.00, 1.99) based on the sensitivity analysis using the November 2017 data from KN189. The ESC considered that, overall, the results did not support the claim that NIVO+IPI+platinum is non-inferior to pembrolizumab+platinum for the patient relevant outcome of OS.

6.23 The PSCR disagreed with using the upper 95% CI of the OS HR for assessing non-inferiority, considering it to be overly conservative. Further, the PSCR argued that the approach to assessing non-inferiority based on the upper 95% CI being <1.32 or <1.30 would represent a substantial deviation from precedent non-inferiority margins accepted by the PBAC, including the assessment of non-inferiority of pembrolizumab versus nivolumab as treatment for BRAFV600 positive melanoma in March 2020. The PSCR noted upper 95% CI bound of the OS HR for NIVO+IPI+platinum versus pembrolizumab+platinum in NSCLC range from 1.23-1.69, which are less than the upper 95% CI reported for pembrolizumab versus nivolumab in BRAFV600 positive melanoma of 1.99 which was accepted by the PBAC as supporting a claim of non-inferiority. The ESC noted that non-inferiority is not determined by one outcome in isolation but is considered in the context of all available information. The ESC noted that, in addition to the upper 95% CI, the point estimate and whether it exceeds 1 (and by how far) are also important considerations.

6.24 The results of the indirect comparison of OS for NIVO+IPI+platinum versus pembrolizumab+platinum in patients with squamous metastatic NSCLC are presented in Table 8.

Table 8: Adjusted indirect comparison of OS, NIVO+IPI+platinum vs pembrolizumab+platinum, squamous NSCLC

	CheckMate 9LA		Keynote 407	
	NIVO+IPI+platinum	**Platinum chemo**	**PEMBRO+platinum**	**Placebo+ platinum**
ITT analysis				
Population	All histology		Squamous	
Median follow-up	14.2 months	10.9 months	14.3 months	
	N=361	N=358	N=278	N=281
Patients with event, n (%)	190 (52.6%)	242 (67.6%)	168 (60.4%)	197 (70.1%)
Median OS (95%CI), months	15.6 (13.9, 20.0)	10.9 (9.5, 12.6)	17.1 (14.4, 19.9)	11.6 (10.1, 13.7)
HR (95%CI)	0.66 (0.55, 0.80)		0.71 (0.58, 0.88)	
12-month OS rate	62.9%	46.9%	64.7%	49.6%
Indirect estimate of effect, HR (95% CI)[a]			**0.93 (0.70, 1.23)**	
Supplementary analysis: squamous subgroup CM9LA				
Population	Squamous subgroup		Squamous	
Median follow-up	14.2 months	10.9 months	14.3 months	
	N=115	N=112	N=278	N=281
Patients with event, n (%)	66 (57.4%)	83 (74.1%)	168 (60.4%)	197 (70.1%)
Median OS (95%CI), months	14.5 (13.1, 19.4)	9.1 (7.2, 11.6)	17.1 (14.4, 19.9)	11.6 (10.1, 13.7)
HR (95%CI)	0.62 (0.45, 0.86)		0.71 (0.58, 0.88)	
12-month OS rate	63.5%	40.0%	64.7%	49.6%
Indirect estimate of effect, HR (95% CI)[a]			**0.87 (0.59, 1.28)**	

Source: Table 84, p160 of the submission.

Chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; ITC = indirect treatment comparison; ITT = intention to treat; NIVO= nivolumab; OS = overall survival; PEMBRO = pembrolizumab

[a] Adjusted for the common reference.

[b] The HR for OS in KN407 for the ITT population at median follow-up of 7.8 months (November 2017 data cut-off) was 0.64 (0.49, 0.85)

6.25 The submission stated that the indirectly derived HRs for OS for the primary analysis (CM9LA ITT: HR 0.93) and the supplementary analysis (squamous subgroup CM9LA: HR 0.87) were both less than the proposed non-inferiority margin of 1.30 for squamous NSCLC. On this basis, the submission claimed that, in patients with squamous NSCLC, NIVO+IPI+platinum is non-inferior to pembrolizumab+platinum for the patient relevant outcome of OS. As stated above, it is not appropriate to use the point estimate of the indirectly derived HR to evaluate non-inferiority.

6.26 The ESC noted the upper 95% CI for the OS HR for the primary analysis (CM9LA ITT: 1.23) and the supplementary analysis (squamous subgroup CM9LA: 1.28) were both less than the proposed non-inferiority margin of 1.30 for squamous NSCLC. On this basis, the ESC considered the submission's claim that, NIVO+IPI+platinum is non-inferior to pembrolizumab+platinum for the patient relevant outcome of OS in patients with squamous NSCLC may be reasonable.

NIVO+IPI+platinum versus atezolizumab+bevacizumab+platinum

6.27 In the absence of a common comparator arm, the submission presented a naïve indirect comparison of NIVO+IPI+platinum and atezolizumab+bevacizumab+platinum, based on the outcome of median OS from CM9LA and IMpower150.

6.28 The submission stated that, compared with CM9LA, IMpower150 reported a greater proportion of patients with PD-L1 TPS <1% (40% versus 47%). However, it also noted

that IMpower150 applied a different PD-L1 expression scoring system compared with that used in CM9LA. There were insufficient details available for the IMpower150 trial to allow an adequate assessment of the potential for confounding. Furthermore, in an unadjusted indirect comparison of single treatment arms, it is not possible to use the event rate in a common reference arm to assess and adjust for any imbalances in both observed and unobserved confounding factors that may exist. Therefore, the results of the indirect comparison should be interpreted with caution.

6.29 A comparison of the OS outcomes in the NIVO+IPI+platinum arm of CM9LA and the atezolizumab+bevacizumab+platinum arm of IMpower150 is presented below.

Table 9: Unadjusted indirect comparison of OS, NIVO+IPI+platinum vs atezolizumab+bevacizumab+platinum

	NIVO+IPI+platinum (CheckMate 9LA)		**ATEZO+BEVA+platinum (IMpower 150)**		
Median follow-up	14.2 months		39.3 months *(20 months)*[ba]		
	Patients with event n/N (%)	Median OS (95% CI)	Patients with event n/N (%)	Median OS (95% CI)	Difference in median OS
CM9LA: (NSQ+SQ) Impower150: ITT-WT (NSQ)	190/361 (53%)	15.6 (13.9, 20.0)	NR *179/359 (50%)*	19.5 (17.0, 22.2) *19.2 (17.0, 23.8)*	-3.9 months *-3.6 months*
CM9LA: NSQ only Impower150: ITT-WT (NSQ)	124/246 (50%)	17.0 (14.0, NE)	NR *179/359 (50%)*	19.5 (17.0, 22.2) *19.2 (17.0, 23.8)*	-2.5 months *-2.2 months*

Source: Table 92 p169 and Table 93 p170 of the submission; Socinski et al (2018).

ATEZO = atezolizumab; BEVA = bevacizumab; CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; ITC = indirect treatment comparison; ITT-WT = intention to treat wild type; NIVO= nivolumab; NE = not evaluable; NR = not reported; NSQ = non-squamous; OS = overall survival; SQ = squamous.

[a] The submission presented the median OS from the September 2019 data cut-off (median follow-up 39.3 months). The results from the interim analysis of OS (data cut-off January 2018) are also presented as the duration of follow-up (20 months) was more consistent with that in CM9LA.

Figures in italics are from the January 2018 data cut-off for IMpower 150. These are the data on which the PBAC's recommendation to list atezolizumab+bevacizumab+platinum was based (Atezolizumab plus bevacizumab PSD, March 2019 PBAC meeting).

6.30 The submission stated that, as the difference in the median OS reported for NIVO+IPI+platinum and atezolizumab+bevacizumab+platinum, in both the primary analysis and the supplementary analysis were both within the proposed non-inferiority margin of ± 4 months, it inferred that NIVO+IPI+platinum was non-inferior to atezolizumab+bevacizumab+platinum for the patient relevant outcome of OS. The comparison of the median OS is relatively uninformative, as median OS represents only one point on the Kaplan-Meier curve. As above, the fact that the point estimate of the difference in the outcomes between the treatment arms lies within the non-inferiority margin is not sufficient to support a claim of non-inferiority. In order to demonstrate non-inferiority, it is necessary to estimate the confidence interval for the difference in OS and the lower boundary of the 95% CI for the comparative treatment effect must be within the predefined non-inferiority margin to establish non-inferiority.

6.31 The ESC agreed with the evaluation that due to the considerable potential for confounding in the unadjusted indirect comparison, the uninformative nature of the outcome used in the indirect comparison (median OS), and the absence of a reliable estimate of the confidence interval associated with the indirectly derived comparative

treatment effect, it is difficult to draw any reliable conclusions regarding the comparative effectiveness of NIVO+IPI+platinum and atezolizumab+bevacizumab+platinum in this patient population.

6.32 The PSCR acknowledged that there are several parameters limiting the robustness of an adjusted indirect comparison between NIVO+IPI+platinum and atezolizumab+bevacizumab+platinum, however the Sponsor considered this justified the presentation of a naïve indirect comparison in the submission. The PSCR included the results of an adjusted indirect treatment comparison presented in overseas reimbursement submissions for consideration by the PBAC, which it considered supported a claim of non-inferiority of NIVO+IPI+platinum and atezolizumab+bevacizumab+platinum, given the point estimate and upper 95% CI for the indirect comparison of OS HR are all below the proposed non-inferiority margin for non-squamous NSCLC of 1.32. The ESC noted this analysis had not been evaluated.

Comparative harms

6.33 A comparison of key adverse events across the NIVO+IPI+platinum and pembrolizumab+platinum trials is provided below.

Table 10: Comparison of key adverse events across the NIVO+IPI+platinum and pembrolizumab+platinum trials

	NIVO+IPI+platinum		Pembrolizumab+platinum	
Trial ID	**CM9LA (ITT)**		**KN189 (non-squamous NSCLC)**	
	NIVO+IPI+platinum N=358	**Platinum chemo N=349**	**PEMBRO+platinum N=405**	**Placebo+platinum N=202**
Population	All histology		Non-squamous	
Median follow-up	14.2 months[b]	10.9 months[b]	23.1 months	
AEs of any causality	n (%)	n (%)	n (%)	n (%)
Any AE				
Any grade	356 (99.4)	342 (98.0)	404 (99.8)	200 (99.0)
Grade 3-4/5[a]	245 (68.4)	188 (53.9)	291 (71.9)	135 (66.8)
AE leading to discontinuation				
Any grade	101 (28.2)	61 (17.5)	136 (33.6)[c]	33 (16.3)[c]
Grade 3-4	81 (22.6)	43 (12.3)	NR	NR
Death due to AE	NR	NR	29 (7.2)	14 (6.9)
Death due to TRAE	7 (2.0)	6 (1.8)	NR	NR
Trial ID	**CM9LA (ITT)**		**KN407 (squamous NSCLC)**	
	NIVO+IPI+platinum N=358	**Platinum chemo N=349**	**PEMBRO+platinum N=405**	**Placebo+platinum N=202**
Population	All histology		Squamous	
Median follow-up	14.2 months[b]	10.9 months[b]	14.3 months[d]	
AEs of any causality	n (%)	n (%)	n (%)	n (%)
Any AE				
Any grade	356 (99.4)	342 (98.0)	274 (98.6)	275 (98.2)
Grade 3-4/5[a]	245 (68.4)	188 (53.9)	206 (74.1)	195 (69.6)
AE leading to discontinuation				
Any grade	101 (28.2)	61 (17.5)	76 (27.3)	37 (13.2)
Grade 3-4	81 (22.6)	43 (12.3)	NR	NR
Death due to AE	NR	NR	31 (11.2)	19 (6.8)
Death due to TRAE	7 (2.0)	6 (1.8)	12 (4.3)	5 (1.8)

Source: Table 102 p178, Table 106 p183 and Table 109 p 189 of the submission; Table 7.1-1 p120-122 and Table 7.2-1 p123, CheckMate 9LA updated analysis CSR; Table 3, Gadgeel et al (2020); Table 3 Paz-Ares et al (2020).

AE = adverse event; IPI = ipilimumab; ITT = intention to treat; NIVO = nivolumab; NR = not reported; NSCLC = non-small cell lung cancer; PEMBRO = pembrolizumab; TRAE = treatment-related adverse event.

[a] CheckMate 9LA reported Grade 3-4 AEs, Keynote 189 and Keynote 407 reported Grade 3-5 AEs; Table 3, Paz-Ares et al (2020).

[b] February 2020 data cut-off

[c] Event leading to discontinuation of any treatment component

[d] May 2019 data cut-off. Source: Paz-Ares et al (2020).

6.34 The submission noted the following differences in the rate of adverse events (AEs) in the immunotherapy arms of CM9LA and KN189:

- AEs ≥ Grade 3: a 4% risk reduction for patients receiving NIVO+IPI+platinum (68%) compared with patients treated with pembrolizumab+platinum in KN189 (72%) and a 6% risk reduction compared patient in KN407 (74%). The 68% reported for CM9LA was only Grade 3-4 AEs, while KN189 and KN407 reported Grade 3-5 AEs.
- AEs of any causality resulting in treatment discontinuation, with a 6% risk reduction for patients treated with NIVO+IPI+platinum (28%) compared with patients treated with pembrolizumab+platinum (34%); and
- AEs leading to death, with a 5% risk reduction for patients treated with NIVO+IPI+platinum (2%) compared with patients treated with

pembrolizumab+platinum in KN189 (7%) and a 9% risk reduction compared to patients in KN407 (11%). It is inappropriate to compare these statistics as CM9LA reported deaths due to drug toxicity while KN189 and KN 407 reported deaths due to AEs of any causality. Treatment related deaths (Grade 5 AEs) were reported in 12/278 (4%) of patients in the pembrolizumab+platinum arm of KN407 (Paz-Ares et al, 2020).

6.35 There was no clear indication of any major difference in the rate of Grade ≥3 AEs or AEs leading to discontinuation across the trials. While the rate of some immune-mediated AEs differed across the trials, these should be interpreted with caution given the considerable potential for confounding in any comparison of AE event rates across trials.

6.36 The submission claimed that, compared with pembrolizumab+platinum, NIVO+IPI+platinum was associated with lower rates of AEs, including Grade 3-4 AEs, associated with the use of platinum chemotherapy, such as anaemia and neutropenia. Given that only two cycles of platinum-based chemotherapy are administered in combination with nivolumab plus ipilimumab, compared to four cycles when administered in combination with pembrolizumab, it was reasonable to expect that there would be fewer AEs associated with platinum-based chemotherapy. However there is potential for more immunological AEs related to immunotherapy with NIVO+IPI+platinum compared with pembrolizumab+platinum.

6.37 The ESC considered the claim of non-inferior safety may be premature, given the follow-up for the NIVO+IPI+platinum trial was substantially shorter than that of the pembrolizumab+platinum trials. The ESC noted that immunological AEs can often have a delayed onset and in the context of continuous co-administration of NIVO+IPI versus pembrolizumab (post-chemotherapy), the AEs of NIVO+IPI may be underestimated.

Benefits/harms

6.38 The submission claimed that NIVO+IPI+platinum is non-inferior, in terms of both comparative effectiveness and safety, to both pembrolizumab+platinum and atezolizumab+bevacizumab+platinum. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.39 The submission described NIVO+IPI+platinum as non-inferior in terms of both effectiveness and safety compared to pembrolizumab+platinum. The evaluation considered that while the claim that NIVO+IPI+platinum was non-inferior to pembrolizumab+platinum in terms of comparative safety was reasonable, the claim regarding the comparative effectiveness was not adequately supported:

- For the comparison of CM9LA (non-squamous and squamous NSCLC) and KN189 (non-squamous NSCLC):

- The median duration of follow-up in CM9LA (14.2 months in the NIVO+IPI+platinum and 10.9 months in the platinum chemotherapy arm) was considerably shorter than the duration of follow-up in KN189 (23.1 months). The indirect comparison was likely to be confounded by this difference in the duration of follow-up between the trials;
- The indirectly derived HR for OS based on the ITT populations of the trials was 1.18 (95% CI: 0.88, 1.58), while that based on the comparison of the non-squamous subgroup from CM9LA and the ITT population of KN189 was 1.23 (95% CI: 0.90, 1.69). The upper limit of the 95% CI in both comparisons exceeded the nominated non-inferior margin of 1.32. The PBAC noted the indirectly derived HR for OS for non-squamous NSCLC favoured pembrolizumab+platinum for both comparisons (i.e., HR >1).

- For the comparison CM9LA (non-squamous and squamous NSCLC) and KN407 (squamous NSCLC):
  - The indirectly derived HR for OS based on the ITT populations of the trials was 0.93 (95% CI: 0.70, 1.23), while that based on the comparison of the squamous subgroup form CM9LA and the ITT population of KN407 was 0.87 (95% CI: 0.59, 1.28). The upper limit of the 95% CI (1.23) was below the non-inferiority margin proposed by the submission (1.30).

6.40 The ESC considered that the claim of non-inferior comparative effectiveness of NIVO+IPI+platinum versus pembrolizumab+platinum was not adequately supported in the non-squamous NSCLC patient population, but may be adequately supported in the squamous NSCLC patient population. The ESC considered that further follow-up data from the CM9LA trial would be informative.

6.41 The ESC considered the claim of non-inferior comparative safety for NIVO+IPI+platinum versus pembrolizumab+platinum was not adequately supported by the data presented in the submission (paragraph 6.37).

6.42 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable for the squamous population but was not adequately supported by the data for the non-squamous population.

6.43 The PBAC considered that the claim of non-inferior comparative safety was supported by the clinical data provided in the submission but was uncertain in the longer term.

Economic analysis

6.44 The submission presented a cost minimisation analysis (CMA) of NIVO+IPI+platinum versus pembrolizumab+platinum. The ESC considered that the claim of non-inferior comparative effectiveness was not adequately supported for patients with non-squamous NSCLC and therefore a CMA was not appropriate for this population which the submission estimated accounted for 77.6% of the total population.

6.45 The key components of the CMA are presented in Table 11. The equi-effective doses were based on the doses and the truncated mean duration of treatment used in the

key clinical trials. As appropriate data on the duration of treatment in KN407 were not available for the data cut-off used for the indirect comparison (May 2019), the submission used the duration of treatment from the April 2018 data cut-off (median duration of follow-up 7.8 months).

Table 11: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption			
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, effectiveness is assumed to be non-inferior. This claim was poorly supported by the clinical evidence presented in the submission.			
Therapeutic claim: safety	Based on evidence presented in Section 2, safety is assumed to be non-inferior.			
Evidence base	Indirect comparison of NIVO+IPI+platinum and pembrolizumab+platinum.			
Equi-effective doses	Dose	Doses	Dose	Doses
Non-squamous NSCLC[a]	Nivolumab 360 mg Q3W Ipilimumab 72.55 mg Q6W Pemetrexed 905 mg Q3W Carboplatin 600 mg Q3W, or cisplatin 136 mg Q3W[b]	11.7 6.0 1.9 1.9 1.9	Pembro/pemetrexed/carboplatin[c] Pembrolizumab 200 mg Q3W pemetrexed 905 mg Q3W Carboplatin 600 mg Q3W OR Pembro/pemetrexed/cisplatin[c] Pembrolizumab 200 mg Q3W pemetrexed 905 mg Q3W Cisplatin 136 mg Q3W	13.4 11.2 3.6 14.4 13.0 3.6
Squamous NSCLC[a]	Nivolumab 360 mg Q3W Ipilimumab 72.55 mg Q6W Paclitaxel 374 mg Q3W Carboplatin 600 mg Q3W	11.7 6.0 1.9 1.9	Pembrolizumab 200 mg Q3W Paclitaxel 374 mg Q3W Carboplatin 600 mg Q3W	9.6 3.6 3.7
Direct medicine costs	As special pricing arrangements apply to pembrolizumab, the submission applied an assumed 30% rebate on the published price. The total direct medicine costs per patient per course were marginally higher for NIVO+IPI+platinum (effective AEMP $[redacted])[d] than for pembrolizumab+platinum (assumed effective AEMP $[redacted]).			
Other costs or cost offsets	Yes Administration costs			

Source: Table 124, p 214-215 of the submission.
AEMP = approved ex-manufacturer price; IPI = ipilimumab; NIVO = nivolumab; NSCLC = non-small cell lung cancer; Q3W = every 3 weeks; Q6W = every 6 weeks.
[a] Assumed 77.6% of patients have non-squamous NSCLC and 22.4% have squamous NSCLC
[b] Assumed 70% of patients received carboplatin and 30% received cisplatin, based on usage in CM9LA
[c] Assumed 72.2% received carboplatin and 27.8% received cisplatin, as in KN189.
[d] The effective prices were derived in the cost-minimisation analysis based on an assumed 30% rebate for pembrolizumab and are only a placeholder.

6.46 The dose regimens in the proposed equi-effective doses were consistent with those used in the clinical trials and the respective PI documents. The dosage of each component of the platinum-doublet chemotherapy regimens used in the CMA were consistent with Cancer Institute of NSW eviQ recommendations for each regimen[‡], as well as with those used in the key trials.

6.47 The proposed equi-effective duration of therapy (number of doses per patient per course) for NIVO+IPI+platinum and pembrolizumab+platinum was based on the mean duration of treatment for each drug from CM9LA (March 2020 data cut-off), KN189

[‡] Source: www.eviq.org.au

(September 2018 data cut-off) and KN407 (April 2018 data cut-off). At the data cut-offs from which the mean duration of treatment was sourced, 21% of patients in the NIVO+IPI+platinum arm of CM9LA, 14% of patients in the pembrolizumab+platinum arm of KN189 and 44% of patients in the pembrolizumab+platinum arm of KN407 were still receiving at least one component of randomised treatment. Therefore, the duration of therapy used in the cost-minimisation analysis for ongoing components of the treatment regimens (i.e. nivolumab, ipilimumab, pembrolizumab, and pemetrexed maintenance therapy) were truncated mean durations, and their use will have underestimated the true mean duration of treatment for each of these components. The PSCR acknowledged this issue and stated its willingness to work with the Department of Health post-PBAC recommendation to ensure that the most up-to-date and appropriate duration of therapy from the CM9LA trial is applied to derive an equi-effective cost per patient per treatment course versus pembrolizumab+platinum.

6.48 The submission noted that the limited duration of follow-up in KN407 will have underestimated the mean number of doses of pembrolizumab+platinum in patients with squamous NSCLC, and that this would have biased the results of the CMA against NIVO+IPI+platinum. While this was reasonable, a greater proportion of patients were still receiving randomised treatment in the NIVO+IPI+platinum arm of CM9LA (21%) compared with the pembrolizumab+platinum arm of KN189 (14%). Therefore, the extent of the underestimation of the true mean duration of therapy in patients with non-squamous NSCLC, who account for approximately 78% of the first-line Stage IV NSCLC population, is likely to be greater for NIVO+IPI+platinum than for pembrolizumab+platinum, potentially favouring NIVO+IPI+platinum.

6.49 Given the disparities in the maturity of the duration of treatment data across the trials, the equi-effective doses of NIVO+IPI+platinum and pembrolizumab+platinum are uncertain.

6.50 The submission assumed that 77.6% of patients have non-squamous NSCLC and 22.4% have squamous NSCLC. This is consistent with the proportions used in the estimated PBS usage and financial implications in the July 2019 submission for pembrolizumab+platinum (Table 19, pembrolizumab NSCLC PSD, July 2019 PBAC Meeting). These estimates were originally sourced from the Australian cohort (n=208) in a multinational retrospective cohort of treatment patterns in patients with Stage IIIB/IV NSCLC.[§]

6.51 The submission included the costs of intravenous administration. For the initial phase of NIVO+IPI+platinum and pembrolizumab+platinum, when nivolumab ± ipilimumab or pembrolizumab were administered in combination with platinum-doublet chemotherapy, an administration cost of $84.60 (85% benefit MBS item 13918) was applied. For the remaining infusions of nivolumab ± ipilimumab and pembrolizumab ±

[§] de Castro J, Tagliaferri P*, et al.* Systemic therapy treatment patterns in patients with advanced non-small cell lung cancer (NSCLC): PIvOTAL study. *Eur J Cancer Care (Engl)*. 2017; 26 (6).

pemetrexed, an administration cost of $56.20 (85% benefit MBS item 13915) was applied. The submission should have used the full MBS fee for these items.

6.52 As a SPA applies to pembrolizumab for the treatment of metastatic NSCLC, the submission applied an assumed SPA rebate of 30% to the published approved ex-manufacturer price (AEMP) for pembrolizumab (i.e. an assumed effective AEMP of $2,965.90/100 mg vial). The submission stated that the sponsor proposed that the effective price for nivolumab in the first-line setting be equivalent to the effective price in the second-line setting (AEMP $[redacted]/100 mg vial). This was used to determine the proportion of the overall treatment cost per patient per course attributable to the nivolumab component.

6.53 The overall cost of the ipilimumab component of the treatment regimen was derived in the CMA, as presented in Table 12, and the effective AEMP per 50 mg vial of ipilimumab ($[redacted]) was subsequently derived as in Table 13.

Table 12: Results of the cost-minimisation analysis – cost/patient/course (assumed effective AEMP)

Component	NIVO+IPI+platinum	Pembrolizumab+platinum
Medicine costs		
Nivolumab	$[redacted]	-
Ipilimumab	$[redacted][a]	-
Pembrolizumab	-	$[redacted]
Platinum chemotherapy	$211.79	$839.67[a]
Total medicine cost/patient/course	$[redacted][a]	$[redacted][a]
Administration costs	$849.48[b]	$983.64[b]
Total cost per patient per course	$[redacted][a, b]	$[redacted][a, b]

Source: Table 131 p226, Table 132 p227 and Table 133 p228 of the submission; Excel workbook 'Section 3 – 1L NSCLC Nivo+Ipi+Chemo Cost-Minimisation Analysis.'
AEMP = approved ex-manufacturer price; IPI = ipilimumab; NIVO = nivolumab
[a] Corrected figures: there was a calculation error in cells E8:F9, Spreadsheet 'SQ CMA' of the section 3 Excel workbook. The price per milligram for paclitaxel had been derived by dividing the price for 400 mg by the dose of carboplatin (600 mg) in C14 'SQ dosing and Assumptions', and the price per milligram for carboplatin had been derived by dividing the cost for 600 mg by the dose of paclitaxel (374 mg) in C15 ''SQ dosing and Assumptions'.
[b] Applying the full MBS fee as of July 2020 of $67.10 for MBS item 13915 and $101.00 for MBS item 13918.

Table 13: Cost-minimised price for nivolumab and ipilimumab (assumed effective AEMP)[a]

	Unit	Unit cost Effective AEMP	Dose	Effective AEMP/dose	Duration treatment (doses)	Total effective cost
Nivolumab	100 mg	**$[redacted]**	360 mg	$[redacted]	11.7	$[redacted]
	40 mg	**$[redacted]**				
Ipilimumab	50 mg	**$[redacted]**	72.55 mg	$[redacted]	6.0	$[redacted]
Total						$[redacted]

Source: Table 132, p227 of the submission; Excel workbook 'Section 3 – 1L NSCLC Nivo+Ipi+Chemo Cost-Minimisation Analysis.'
AEMP = approved ex-manufacturer price
[a] Corrected figures as described for Table 12
Figures in bold are the cost-minimised effective AEMP for nivolumab and ipilimumab.

6.54 The key source of uncertainty in the CMA was the extent of underestimation of the true duration of therapy resulting from the use of the truncated mean duration of therapy from the key trials, especially given the immaturity of the data in KN407. To assess the impact of duration of therapy on the outcome of the CMA, the following sensitivity analyses were performed during the evaluation:

i) The mean number of doses per patient per course of nivolumab and pembrolizumab in both non-squamous and squamous NSCLC was assumed to be equal to the mean number of doses for pembrolizumab in KN189 (weighted mean of 13.76 doses)[**]. The number of doses of ipilimumab was adjusted to maintain the ratio of doses of nivolumab:ipilimumab of 11.7:6.0.

ii) The mean number of doses per patient per course of nivolumab and pembrolizumab in both non-squamous and squamous NSCLC was assumed to be equal to the mean number of doses for nivolumab in CM9LA (11.7 doses). The number of doses of pemetrexed when used with pembrolizumab was adjusted to maintain the ratio of doses of pembrolizumab:pemetrexed of 13.76:11.70[††].

6.55 The results of the sensitivity analyses are presented below.

Table 14: Results of the sensitivity analyses – price for nivolumab and ipilimumab based on cost-minimised price (assumed effective AEMP)[a]

	Unit	Unit cost Effective AEMP	Dose	Effective AEMP/dose	Duration treatment (doses)	Total effective cost
Base case - truncated duration of treatment from trials						
Nivolumab	100 mg	**$**	360 mg	$	11.7	$
	40 mg	**$**				
Ipilimumab	50 mg	**$**	72.55 mg	$	6.0	$
Total						$
SA1 – mean duration of treatment for nivolumab and pembrolizumab based on KN189						
Nivolumab	100 mg	**$**	360 mg	$	13.76 [b]	$
	40 mg	**$**				
Ipilimumab	50 mg	**$**	72.55 mg	$	7.06[c]	$
Total						$
SA2 - mean duration of treatment for nivolumab and pembrolizumab based on CM9LA[d]						
Nivolumab	100 mg	**$**	360 mg	$	11.7	$
	40 mg	**$**				
Ipilimumab	50 mg	**$**	72.55 mg	$	6.0	$
Total						$

Source: Table 132, p227 of the submission; Excel workbook 'Section 3 – 1L NSCLC Nivo+Ipi+Chemo Cost-Minimisation Analysis.'
AEMP = approved ex-manufacturer price; SA = sensitivity analysis
[a] Corrected figures as described for Table 12
[b] Weighted mean dose, assuming 72.2% receive carboplatin/pemetrexed and 27.8% receive cisplatin/pemetrexed (72.2% x 13.40 + 27.8% x 14.70)
[c] 7.06 = 6.0 / 11.7 x 13.76
[d] Assuming 11.70 pembrolizumab doses for NSQ and SQ
Figures in bold are the cost-minimised effective AEMP for nivolumab and ipilimumab.

6.56 These results indicate that the use of the truncated mean duration of treatment from the clinical trials favours NIVO+IPI+platinum in the cost-minimisation analysis compared to using a similar duration of treatment for the nivolumab and

[**] Weighted number of doses of pembrolizumab for patients receiving carboplatin/pemetrexed (72.2% x 13.4 doses) and patients receiving cisplatin/pemetrexed (28.2% x 14.7 doses).
[††] Weighted number of doses of pemetrexed for patients receiving carboplatin/pemetrexed (72.2% x 11.2 doses) and patients receiving cisplatin/pemetrexed (28.2% x 13.0 doses).

pembrolizumab components of NIVO+IPI+platinum and pembrolizumab+ platinum, and applying this across both patients with non-squamous NSCLC and those with squamous NSCLC.

6.57 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with NIVO+IPI+platinum would be no more than the cost per patient of pembrolizumab+platinum. The cost per patient takes into account the mean equi-effective doses of the new intervention and the alternative therapy, and also accounts for any difference in the mean duration of treatment. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

Drug cost/patient/course

6.58 The estimated effective AEMP per dose and the effective dispensed price per dose for each component of NIVO+IPI+platinum and pembrolizumab+platinum are summarised in Table 15.

Table 15: Estimated effective AEMP per dose and effective dispensed price per dose

	Dose regimen	Dose	Effective AEMP/dose	Weighted dispensed price/dose[a]
Nivolumab	360 mg Q3W	360 mg	$	$
Ipilimumab	1 mg/kg Q6W	72.55 mg	$ [b]	$ [b]
Pembrolizumab	200 mg Q3W	200 mg	$5,931.80[c]	$6,100.38
Pemetrexed	500 mg/m^2 Q3W	905 mg	$69.35	$182.11
Carboplatin	AUC 6 Q3W	600 mg	$48.92	$161.49
Cisplatin	75 mg/m^2 Q3W	136 mg	$26.92[d]	$139.27
Paclitaxel	100 mg/m^2 Q3W	374 mg	$61.91	$174.60

Source: Excel workbook 'Section 3 – 1L NSCLC Nivo+Ipi+Chemo Cost-Minimisation Analysis; Excel Workbook 'Section 4 – 1L NSCLC Nivo+Ipi+Chemo Utilisation and Cost Model'.

AEMP = approved ex-manufacturer price; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] Assuming 32%/68% public/private split.

[b] After applying corrections in the CMA

[c] Assumed effective AEMP for pembrolizumab

[d] In the cost-minimisation analysis, the AEMP per dose for cisplatin was $26.87. Due to rounding applied to the mean dose of cisplatin in the Section 4 workbook, the AEMP per dose was $29.92.

6.59 The estimated weighted mean number of doses per patient per course, and the cost per patient per course, are summarised in Table 16.

Table 16: Drug cost per patient for NIVO+IPI+platinum and pembrolizumab+platinum (assumed effective dispensed price)

	NIVO+IPI+platinum		Pembrolizumab+platinum	
	Trial / Model[a]	**Financial estimates[b]**	**Trial / Model[c]**	**Financial estimates[d]**
Mean doses	Nivolumab: 11.7 Ipilimumab: 6.0 Pemetrexed: 1.47 Carboplatin: 1.46 Cisplatin: 0.44 Paclitaxel: 0.43	Nivolumab: 11.7 Ipilimumab: 6.0 Pemetrexed: 1.51 Carboplatin: 1.29 Cisplatin: 0.39 Paclitaxel: 0.61	Pembrolizumab: 12.83 Pemetrexed: 9.08 Carboplatin: 2.85 Cisplatin: 0.78 Paclitaxel: 0.81	Pembrolizumab: 12.43 Pemetrexed: 7.96 Carboplatin: 2.95 Cisplatin: 0.68 Paclitaxel: 0.81
Cost/patient/ course (effective dispensed price)	Nivolumab: $[redacted] Ipilimumab: $[redacted][e] Pemetrexed: $269 Carboplatin: $235 Cisplatin: $62 Paclitaxel: $74 TOTAL: $[redacted]	Nivolumab: $[redacted] Ipilimumab: $[redacted] Pemetrexed: $275 Carboplatin: $209 Cisplatin: $54 Paclitaxel: $106 TOTAL: $[redacted]	Pembrolizumab: $[redacted] Pemetrexed: $[redacted] Carboplatin: $460 Cisplatin: $108 Paclitaxel: $141 TOTAL: $[redacted]	Pembrolizumab: $[redacted] Pemetrexed: $[redacted] Carboplatin: $477 Cisplatin: $95 Paclitaxel: $141 TOTAL: $[redacted]

Source: Excel workbook 'Section 3 – 1L NSCLC Nivo+Ipi+Chemo Cost-Minimisation Analysis; Excel Workbook 'Section 4 – 1L NSCLC Nivo+Ipi+Chemo Utilisation and Cost Model'.

IPI = ipilimumab; NIVO = nivolumab

[a] Weighted dose from trial (see Table 11), assuming 77.6% of patients have non-squamous NSCLC and 22.4% have squamous NSCLC, and carboplatin/cisplatin split of 70%/30% in patients with non-squamous NSCLC.

[b] Weighted dose from trial (see Table 11), assuming 68.0% of patients have non-squamous NSCLC and 32.0% have squamous NSCLC, and carboplatin/cisplatin split of 70%/30% in patients with non-squamous NSCLC.

[c] Weighted dose from trial (see Table 11), assuming 77.6% of patients have non-squamous NSCLC and 22.4% have squamous NSCLC, and carboplatin/cisplatin split of 72.2%/27.8% in patients with non-squamous NSCLC.

[d] Weighted dose from trial (see Table 11), assuming 68.0% of patients have non-squamous NSCLC and 32.0% have squamous NSCLC, and carboplatin/cisplatin split of 72.2%/27.8% in patients with non-squamous NSCLC.

[e] Based on corrected price for ipilimumab, as derived in Table 13.

6.60 In both the model and the financial estimates, the mean number of doses per patient for each component of treatment were based on the truncated mean number of doses in the trials (see Table 11). Both the type of chemotherapy received and, for pembrolizumab+platinum, the mean number of doses per patient differed by histological subgroup (non-squamous vs squamous). The weighted mean number of doses per patient in the CMA, as listed in Table 16, were derived assuming that 77.6% of treated patients have non-squamous NSCLC and 22.4% have squamous NSCLC. In the financial estimates, while the proportion of eligible patients with non-squamous and squamous NSCLC was consistent with the CMA (i.e. 77.6% non-squamous and 22.4% squamous) the submission assumed that the market share for NIVO+IPI+platinum would differ in each of these patient subgroups (15% in non-squamous and 20% in squamous NSCLC). As a result, in the treated population, 68% of patients had non-squamous NSCLC and 32% had squamous NSCLC. Consequently, the weighted mean number of doses per patient for each component of treatment and the mean cost per patient per course in the financial estimates differed from those in the CMA.

6.61 The pre-sub-committee response (PSCR) acknowledged the weighted mean number of doses per patient for each component of treatment and the mean cost per patient per course in the financial estimates were inconsistent with those presented in the CMA. The Sponsor indicated a willingness to work with the Department to set an

equivalent weighted cost per patient per treatment course, with application of histology based costs per patient to derive the weighted price for nivo+ipi+chemo to ensure cost-neutrality is achieved post-PBAC recommendation.

Estimated PBS usage & financial implications

6.62 This submission was not considered by DUSC. The submission used an epidemiological approach for the financial analysis. The key inputs for the financial estimate are summarised in Table 17.

Table 17: Key inputs for financial estimates

Data	Value applied and source			Comment
Eligible population				
Incidence of lung cancer	49.4/100,000 persons (ACIM lung cancer workbook)			Possibly overestimate. In 'Cancer in Australia 2019' (AIHW), the estimated incidence of lung cancer was 41.2/100,000 persons[a]
% meeting other PBS criteria	86.6% of lung cancer is NSCLC (AIHW 2011) 51.5% Stage IV (Mitchell 2013) 77.6% non-squamous, 22.4% squamous (PIvOTAL study) 18.1% EGFR/ALK/ROS1 positive (Table 19, Pembrolizumab PSD, July 2019 PBAC Meeting). 63.3% ECOG PS 0-1 (Mitchell 2013)			The requested restriction does not exclude use in patients with ROS1 mutation. DUSC[b] estimated that the prevalence of EGFR mutations in the tested and treated NSCLC population in 2015-2016 was 17.9%, therefore the proportion of patients with EGFR, ALK or ROS1 mutation may be an underestimate.
Grandfathered patients	Equivalent patients at full duration of therapy: Yr 1: <500[1] Assumption			Affects estimates in Year 1 only. This estimate was highly uncertain.
Treatment utilisation				
Proportion electing treatment	95%. Assumption			These inputs were highly uncertain. The submission did not give any justification for the assumed market share of NIVO+IPI+platinum.
Market share NIVO+IPI+platinum	Non-squamous: 15% Squamous: 20% Assumption			
Doses per patient per course	Mean number of doses from trials. See Table 11.			The mean number of doses of each drug was consistent with the CMA. The use of the truncated mean duration of treatment from the trials was discussed above.
Number of infusions	MBS item 13918 (1-6 hrs)/MBS item 13915 (< 1 hr) NIVO+IPI+platinum: 1.9 / 9.8 Pembrolizumab+platinum: 3.6 / 9.23[c]			This was consistent with the CMA.
Costs				
Private/public split	68%/32%	PBS statistics for pembrolizumab+platinum[d]		
PBS/RPBS split	98.6%/1.4%			
Patient copayment	PBS: $24.02 RPBS: $6.27			
Drug costs	Dose	Weighted dispensed price (effective)	Weighted doses per course	
Nivolumab	360 mg	$[redacted]	11.7	
Ipilimumab	72.55 mg	$[redacted]	6.0	
Pembrolizumab	200 mg	$6,100.38	12.83	Assumed 30% rebate on published AEMP

Data	Value applied and source			Comment
Pemetrexed	600/905 mg[d]	$150.77/$182.11	11.7	The submission made a number of errors when calculating the cost of platinum-doublet chemotherapy. These were corrected during the evaluation to align with those used in the CMA.[e]
Carboplatin	600 mg	$159.87 $161.49	3.62	
Cisplatin	75 mg 136 mg	$126.70 $139.27	3.62	
Paclitaxel	200mg 374mg	$145.52 $174.60	3.62	

Source: Table 134, pp231-233 of the submission; Excel Workbook 'Section 4 – 1L NSCLC Nivo+Ipi+Chemo Utilisation and Cost Model'.
ABS = Australian Bureau of Statistics; ACIM = Australian Cancer Incidence and Mortality; AEMP = approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; ALK = anaplastic lymphoma kinase; CMA = cost-minimisation analysis; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; IPI = ipilimumab; NIVO = nivolumab; NSCLC = non-small cell lung cancer; ROS1 = c-ROS proto-oncogene 1

[a] Source: https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2019/data

[b] Erlotinib and gefitinib: 24 month predicted versus actual analysis, Public Release Document, February 2017 DUSC meeting.

[c] The total number of infusions for pembrolizumab+platinum was the weighted average for non-squamous and squamous NSCLC, accounting for the carboplatin/cisplatin split in no-squamous NSCLC. 12.83 = 77.6%*(13.4*72.2%+14.7*27.8%) + 22.4%*9.6.

[d] The submission incorrectly used a dose of 500 mg of pemetrexed when used in combination with nivolumab and ipilimumab, but applied the correct dose (905 mg) when used with pembrolizumab

[e] The difference in the price per dose for cisplatin between the financial estimates and the CMA was due to rounding.

The redacted values correspond to the following range:

[1]<500

6.63 The submission made a number of errors when calculating the change in the number of scripts per year for each component of pembrolizumab+platinum. Firstly, when calculating the weighted number of scripts per patient for pembrolizumab (12.83), it assumed that 77.6% of treated patients have non-squamous NSCLC, while, as explained above, in the financial estimates, 68% had non-squamous disease. Secondly, it incorrectly assumed that all patients received 3.62 doses of carboplatin (only 72.2% of non-squamous patients received carboplatin) and that all non-squamous patients received cisplatin (only 27.8% of non-squamous patients received cisplatin). These were corrected during the evaluation and the re-estimates are presented below.

6.64 The estimated use and financial implications of listing NIVO+IPI+platinum on the PBS/RPBS for first-line treatment of Stage IV NSCLC are summarised below.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Grandfathered patients	[redacted][1]					
Number of scripts dispensed[a]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications of NIVO+IPI+platinum (effective price)						
Cost to PBS/RPBS less copayments[b]	$[redacted][4]	$[redacted][5]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Estimated financial implications for pembrolizumab+platinum (assumed effective price)						
Cost to PBS/RPBS less copayments[b]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][4]	$[redacted][4]
Net financial implications						
Net cost to PBS/RPBS[b]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Net cost to MBS[c]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Net cost to PBS/RPBS/MBS [b, c]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]

Source: Table 135 p235, Table 136 p236, Table 139 p239: Table 143 p243, Table 144 p244, Table 146, p245 and Table 147 p246 of the submission; Excel Workbook 'Section 4 – 1L NSCLC Nivo+Ipi+Chemo Utilisation and Cost Model'.

IPI = ipilimumab; NIVO = nivolumab

[a] Assuming 11.7 nivolumab and 6.0 ipilimumab scripts per patient per year and 1.9 scripts per patient per year for each chemotherapy drug per patient per year, as estimated by the submission.

[b] The submission made a number of errors when calculating the cost of platinum-doublet chemotherapy. These were corrected during the evaluation to align them with the cost per dose in the cost minimisation analysis.

[c] The submission inappropriately included NIVO+IPI+platinum grandfathered patients in Year 1 of the administration costs for pembrolizumab+platinum. This was corrected during the evaluation.

Note: due to an inconsistency in the application of rounding of patient numbers in the Section 4 Excel workbook, the cost-offsets from substitution of pembrolizumab+platinum in Years 5 and 6 may have been underestimated by approximately $[redacted][6] to $[redacted][6] each year.

The redacted values correspond to the following ranges:

[1]*<500*

[2]*500 to <5,000*

[3]*10,000 to <20,000*

[4]*$40 to <$50 million*

[5]*$30 to <$40 million*

[6]*$0 to <$10 million*

[7]*net cost-saving*

6.65 The submission estimated that listing NIVO+IPI+platinum would result in a net cost to the PBS/RPBS of $0 to <$10 million in Year 6. With the inclusion of grandfathered patients in Year 1 of listing, the submission estimated a total cost to the PBS/RPBS of $10 to <$20 million in the first 6 years of listing. The submission's estimates were based on an assumed 30% reduction in the published AEMP for pembrolizumab to reflect the special pricing arrangement for pembrolizumab.

6.66 The submission estimated that there would be up to <500patients receiving first-line treatment with NIVO+IPI+platinum through an access program who may transfer to PBS-listed therapy. The submission noted that these patients would not require the full duration of therapy subsidised on the PBS and estimated that the number of doses of PBS-subsidised nivolumab that these patients would be the equivalent of

approximately <500patients receiving the full course of therapy through the PBS. These estimates were based on a number of poorly supported assumptions and were, therefore, highly uncertain.

6.67 All use of NIVO+IPI+platinum, other than for grandfathered patients, was assumed to substitute for pembrolizumab+platinum. Given this, and that the effective AEMP for NIVO+IPI+platinum was derived based on a cost-minimisation against the assumed effective AEMP for pembrolizumab+platinum, the listing of NIVO+IPI+platinum on the PBS would be expected to be approximately cost-neutral to the PBS/RPBS in Years 2-6. The incremental cost to the PBS/RPBS in the corrected figures for Year 2-6 mainly results from the discrepancy in the relative proportion of patients with non-squamous and squamous NSCLC in the financial estimates (68%:32%) compared to the cost-minimisation analysis (77.6%:22.4%), and the fact that the submission's estimate of the cost per person per course for pembrolizumab+platinum in the CMA was higher for patients with non-squamous NSCLC (assumed effective AEMP: $[redacted]) compared with patient with squamous NSCLC (assumed effective AEMP: $[redacted]).

Financial Management – Risk Sharing Arrangements

6.68 The submission stated that the sponsor was willing to join the current risk-sharing arrangement (with annual subsidisation caps) for NSCLC.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of nivolumab plus ipilimumab in combination with two cycles of platinum-based doublet chemotherapy (NIVO+IPI+platinum) for the treatment of previously untreated Stage IV non-small cell lung cancer (NSCLC), limited to the squamous population only, on the basis that it should be available only under special arrangements under section 100. The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of NIVO+IPI+platinum would be acceptable if it were cost-minimised against pembrolizumab in combination with platinum-based doublet chemotherapy (pembrolizumab+platinum). The PBAC did not recommend NIVO+IPI+platinum for the treatment of previously untreated Stage IV non-squamous NSCLC. The PBAC considered the clinical claim that NIVO+IPI+platinum is non-inferior to pembrolizumab+platinum for efficacy and safety in non-squamous NSCLC was not supported by the clinical evidence presented and therefore a cost-minimisation analysis in this population was not appropriate.

7.2 The PBAC did not consider there to be an unmet clinical need for NIVO+IPI+platinum, as there are currently PBS listed immunotherapies to treat patients with previously untreated stage IV NSCLC. The PBAC considered NIVO+IPI+platinum may provide some patients with a treatment option with less cycles of chemotherapy but noted this perceived benefit would need to be balanced by the ongoing use of ipilimumab.

The PBAC noted that consumers valued additional treatment options, even if there was no difference in clinical outcomes. The PBAC noted NIVO+IPI+platinum does not fulfil the unmet need for treatment options without chemotherapy and NIVO+IPI without chemotherapy was not TGA registered at the time of consideration. . The PBAC noted there are less treatment options for patients with squamous NSCLC and considered an additional treatment option may be useful for some patients.

7.3 The PBAC considered that, given the different duration of follow-up between CM9LA and KN407, it would be reasonable to assume the mean number of doses per patient per course of nivolumab and pembrolizumab in squamous NSCLC was equal to the mean number of doses of pembrolizumab in KN407 (9.6). The number of doses of ipilimumab should be adjusted to maintain the ratio of doses of nivolumab:ipilimumab of 11.7:6.0, consistent with CM9LA. The PBAC considered the equi-effective doses for squamous NSCLC were:

- nivolumab 360 mg every 3 weeks for 9.6 doses, ipilimumab 72.55 mg every 6 weeks for 4.9 doses, paclitaxel 374 mg and carboplatin 600 mg both every 3 weeks for 1.9 doses and
- pembrolizumab 200 mg every 3 weeks for 9.6 doses, paclitaxel 374 mg every 3 weeks for 3.6 doses and carboplatin 600 mg every 3 weeks for 3.7 doses.

7.4 The PBAC advised the restriction criteria for nivolumab and ipilimumab for the treatment of squamous NSCLC should:

- include the clinical criteria “The treatment must be in combination with platinum-based chemotherapy for the first two cycles” in the initial restriction;
- include the clinical criteria “Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition” in the continuing restriction;
- include the clinical criteria “The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma (ALK) gene rearrangement or a c-ROS proto-oncogene 1 (ROS1) gene arrangement in tumour material” in the initial restriction.
- include a restriction for grandfather treatment that will be in place for a period of 12 months after listing.

7.5 The PBAC noted the submission nominated pembrolizumab+platinum as the primary comparator, and atezolizumab plus bevacizumab plus platinum-based doublet chemotherapy (non-squamous NSCLC only) and platinum-based doublet chemotherapy alone as secondary comparators. The PBAC considered the proposed primary and secondary comparators were reasonable.

7.6 The PBAC considered the direct evidence from the Checkmate 9LA study supported the claim that NIVO+IPI+platinum was superior to platinum-based doublet chemotherapy in terms of overall survival (OS), with a hazard ratio (HR) of 0.66 (95%

CI: 0.55, 0.80). The PBAC noted subgroup analyses of the Checkmate 9LA study demonstrated similar relative effects regardless of histology and PD-L1 status but may have less effect in patients over 75 years of age and never-smokers[‡‡].

7.7 The PBAC noted an indirect comparison of NIVO+IPI+platinum compared to pembrolizumab+platinum in non-squamous NSCLC resulted in a HR for OS of 1.18 (95% CI: 0.88, 1.58). The PBAC noted the HR for OS exceeded 1 which suggested a trend towards superior efficacy for pembrolizumab+platinum compared to NIVO+IPI+platinum. The PBAC considered it is clinically plausible that the use of four cycles of chemotherapy with pembrolizumab in patients with non-squamous NSCLC may provide better outcomes than two cycles of chemotherapy with nivolumab and ipilimumab. The PBAC noted the indirect comparison using the subgroup of patients in Checkmate 9LA with non-squamous NSCLC also exceeded 1, favouring pembrolizumab+platinum (OS HR 1.23 (95% CI: 0.90, 1.69). The PBAC considered that, overall, the evidence presented did not support the claim that NIVO+IPI+platinum is of non-inferior effectiveness compared to pembrolizumab+platinum.

7.8 The PBAC noted an indirect comparison of NIVO+IPI+platinum compared to pembrolizumab+platinum in squamous NSCLC resulted in a HR for OS of 0.93 (95% CI: 0.70, 1.23). The PBAC noted a HR for OS of less than 1 suggested a trend towards superior efficacy for NIVO+IPI compared to pembrolizumab+platinum. The PBAC noted squamous NSCLC may be less sensitive to chemotherapy and the use of 2 cycles of chemotherapy with nivolumab and ipilimumab rather than 4 cycles of chemotherapy with pembrolizumab may have less of an impact on outcomes compared to non-squamous NSCLC. The PBAC noted the indirect comparison using the subgroup of patients in Checkmate 9LA with squamous NSCLC was also less than 1 (OS HR 0.87 (95%CI: 0.59, 1.28). The PBAC considered that, overall, the evidence presented supported the claim that NIVO+IPI+platinum is likely to be of non-inferior effectiveness compared to pembrolizumab+platinum.

7.9 The PBAC noted there were no differences in adverse events between NIVO+IPI+platinum and pembrolizumab+platinum but noted the follow-up in the non-squamous pembrolizumab+platinum trial was longer than the NIVO+IPI+platinum trial (23.1 months and 14.2 months, respectively). The PBAC considered the claim of non-inferior safety based on the data presented is reasonable but is uncertain in the longer term because the use of nivolumab in combination with ipilimumab may result in more immunological AEs, compared to pembrolizumab alone, with longer follow-up

7.10 The PBAC noted there were a number of concerns raised by the evaluation regarding the indirect comparison of NIVO+IPI+platinum and atezolizumab + bevacizumab +

[‡‡] Reck M, Ciuleanu TE, Dols MC, et al: Nivolumab plus ipilimumab plus 2 cycles of platinum doublet chemotherapy vs 4 cycles of chemo as first-line treatment for stage IV/recurrent non-small cell lung cancer: CheckMate 9LA. ASCO20 Virtual Scientific Program. Abstract 9501.

chemotherapy (paragraph 6.31) and considered no conclusion regarding the comparative effectiveness and safety could be made.

7.11 The PBAC considered that the equi-effective doses outlined in paragraph 7.3 are an appropriate basis for calculation of the price for NIVO+IPI+platinum for the treatment of squamous NSCLC.

7.12 The PBAC considered that, at a price cost-minimised to pembrolizumab+platinum, the listing of NIVO+IPI+platinum on the PBS for patients with squamous NSCLC would be expected to result in no additional cost to the PBS/RPBS.

7.13 The PBAC advised that NIVO+IPI would need to join the existing RSA caps for NSCLC with no increase to the current caps.

7.14 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because NIVO+IPI+platinum is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over pembrolizumab+platinum for squamous NSCLC, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.

7.15 The PBAC noted that this submission is not eligible for an Independent Review as it was recommended.

Outcome:
Recommended

8 Recommended listing

8.1 Add new indication for nivolumab as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
NIVOLUMAB Injection	NEW (Public) NEW (Private)	360mg	13	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)				

Restriction Summary [new] / Treatment of Concept: [new]

	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): ☒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: Stage IV (metastatic)
	Condition: non-small cell lung cancer (NSCLC)
	Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)
	Treatment Phase: Initial combination treatment (with ipilimumab) as first-line drug therapy
	Clinical criteria:
	The condition must be squamous type non-small cell lung cancer
	AND
	Patient must not have previously been treated for this condition in the metastatic setting
	AND
	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 non-small cell lung cancer.
	AND
	Patient must have a WHO performance status of 0 or 1.
	AND
	The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement or a c-ROS proto-oncogene 1 (ROS1) gene arrangement in tumour material
	AND
	The treatment must be in combination with platinum-based chemotherapy for the first two cycles
	AND
	The treatment must in combination with ipilimumab.
	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.

	Category / Program: Section 100 – Efficient Funding of Chemotherapy
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): ☒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)
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special Pricing Arrangements apply
	Episodicity: [nil]
	Severity: Stage IV (metastatic)
	Condition: non-small cell lung cancer (NSCLC)
	Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)
	Treatment Phase: Continuing combination treatment (with ipilimumab) of first-line drug therapy
	Clinical criteria:
	The condition must be squamous type non-small cell lung cancer
	AND
	Patient must have previously received PBS-subsidised treatment with this drug in this line of treatment
	AND
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition
	AND
	The treatment must not exceed 24 months in total, measured from the initial dose, or, must not extend beyond disease progression, whichever comes first.
	The treatment must be in combination with ipilimumab

	Category / Program: Section 100 – Efficient Funding of Chemotherapy
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): ☒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)
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply
	Administrative Advice: A patient may qualify for PBS-subsidised treatment under this restriction once only.
	Episodicity: [nil]
	Severity: Stage IV (metastatic)
	Condition: non-small cell lung cancer (NSCLC)
	Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)
	Treatment Phase: Grandfather treatment (treatment of a patient commenced on non-PBS subsidised combination treatment as first-line drug therapy)
	Clinical criteria:
	Patient must have received non-PBS subsidised treatment with this drug as first-line drug therapy for this PBS indication prior to [PBS listing date]
	AND
	The condition must be squamous type non-small cell lung cancer
	AND
	Patient must not have developed disease progression while receiving treatment with this drug for this condition
	AND
	Patient must have a WHO performance status of 0 or 1 prior to initiation of non-PBS-subsidised treatment with this drug for this condition
	AND
	The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement or a c-ROS proto-oncogene 1 (ROS1) gene arrangement in tumour material
	AND
	Patient must not have received treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for non-small cell lung cancer prior to initiating treatment with this drug for this PBS indication
	AND
	Patient must not have been treated for this condition in the metastatic setting, prior to initiating non-PBS subsidised treatment with this drug for this condition.
	AND
	The treatment must not exceed 24 months in total, measured from the initial dose, or, must not extend beyond disease progression, whichever comes first
	AND
	The treatment must have been in combination with platinum-based chemotherapy for the first two cycles
	The treatment must be in combination with ipilimumab.

8.2 Add new indication to ipilimumab as follows:

Name, Restriction, Manner of administration and form	**PBS item code**	**Max. Amount**	**№.of Rpts**	**Manufacturer**
IPILIMUMAB Injection	NEW (Public) NEW (Private)	120 mg	4	Bristol-Myers Squibb Australia Pty Ltd
Available brands Yervoy (ipilimumab 50 mg/10 mL injection, 10 mL vial)				

Restriction Summary [new] / Treatment of Concept: [new]

	Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): ☒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)
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special Pricing Arrangements apply
	Condition: non-small cell lung cancer (NSCLC)
	Severity: Stage IV (metastatic)
	Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)
	Treatment Phase: Initial combination treatment (with nivolumab) as first-line drug therapy
	Clinical criteria:
	Patient must not have previously been treated for this condition in the metastatic setting
	AND
	The condition must be squamous type non-small cell lung cancer
	AND
	Patient must have a WHO performance status of 0 or 1
	AND
	The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement or a c-ROS proto-oncogene 1 (ROS1) gene arrangement in tumour material
	AND
	The treatment must be in combination with platinum-based chemotherapy for the first two cycles
	AND
	The treatment must be in combination with nivolumab.
	AND
	Prescribing Instructions:
	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
	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

	Category / Program: Section 100 – Efficient Funding of Chemotherapy
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): ☒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)
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Episodicity: [nil]
	Severity: Stage IV (metastatic)
	Condition: non-small cell lung cancer (NSCLC)
	Treatment Phase: Continuing combination treatment (with nivolumab) of first-line drug therapy
	Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug in this line of treatment.
	AND
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.
	AND
	The treatment must not exceed 24 months in total, measured from the initial dose, or, must not extend beyond disease progression, whichever comes first
	AND
	The treatment must be in combination with nivolumab

	Category / Program: Section 100 – Efficient Funding of Chemotherapy
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): ☒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)
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: A patient may qualify for PBS-subsidised treatment under this restriction once only
	Episodicity: [nil]
	Severity: Stage IV (metastatic)
	Condition: squamous non-small cell lung cancer (NSCLC)
	Treatment Phase: Grandfather treatment (treatment of a patient commenced on non-PBS subsidised combination treatment as first-line drug therapy)
	Clinical criteria:
	Patient must have received non-PBS subsidised treatment with this drug as first-line drug therapy for this PBS indication prior to [PBS listing date].
	AND
	Patient must not have developed disease progression while receiving treatment with this drug for this condition.
	AND
	The condition must be squamous type non-small cell lung cancer
	AND
	Patient must have a WHO performance status of 0 or 1 prior to initiation of non-PBS-subsidised treatment with this drug for this condition.
	AND
	The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement or a c-ROS proto-oncogene 1 (ROS1) gene arrangement in tumour material.
	AND
	Patient must not have had been treated for this condition in the metastatic setting prior to initiating non-PBS subsidised treatment with this drug for this condition.
	AND
	The treatment must not exceed a total of 24 months under this restriction
	AND
	The treatment must have been in combination with platinum-based chemotherapy for the first two cycles
	AND
	The treatment must be in combination with nivolumab.
	Administrative advice:
	This grandfather restriction will cease to operate from 12 months after the date specified in the Clinical criteria.

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 had no comment.