

5.06 CEMIPIMAB, Solution for I.V. infusion 350 mg in 7 mL, Libtayo[®], sanofi-aventis Australia Pty Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 100 (Efficient Funding of Chemotherapy, Streamlined) listing of cemiplimab as first-line treatment of metastatic non-small cell lung cancer (NSCLC), in patients with high expression of programmed cell death ligand 1 (PD-L1), i.e. tumour proportion score (TPS) $\geq 50\%$, who are epidermal growth factor receptor (EGFR) wildtype, negative for anaplastic lymphoma kinase (ALK) or c-ROS proto-oncogene 1 (ROS1) gene rearrangement, and with a World Health Organization (WHO) performance status of 0 or 1.
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) to pembrolizumab. The key components of the clinical issue addressed by the submission are summarised below.

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

Component	Description
Population	Patients with Stage IV (metastatic) NSCLC expressing PD-L1 in $\geq 50\%$ tumour cells with no evidence of an activating EGFR gene or an ALK gene rearrangement or a ROS1 gene arrangement in tumour materials
Intervention	Cemiplimab 350 mg administered Q3W as an IV infusion over 30 minutes, until disease progression or unacceptable toxicity, for a maximum of 24 months.
Comparator	Pembrolizumab 200 mg administered Q3W or 400 mg Q6W as an IV infusion over 30 minutes, until disease progression or unacceptable toxicity, for a maximum of 24 months.
Outcomes	OS, PFS, ORR and safety
Clinical claim	For first-line treatment of patients with Stage IV (metastatic) NSCLC with PD-L1 TPS $\geq 50\%$, cemiplimab is non-inferior to pembrolizumab in terms of efficacy and safety

Source: Table 1.1-1, p1 of the submission

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; IV = intravenous; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; Q3W = every 3 weeks; Q6W = every 6 weeks; ROS1 = c-ROS proto-oncogene 1.

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** not registered. The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Delegate's Overview and Advisory Committee on Medicines (ACM) minutes were available.

- 2.2 The ACM considered cemiplimab to have an overall positive benefit-risk profile for the treatment of adult patients with NSCLC expressing PD-L1 (in $\geq 50\%$ tumour cells) as determined by a validated test and with no EGFR, ALK or ROS1 aberrations, who have
- locally advanced NSCLC and who are not candidates for surgical resection or definitive chemoradiation, or have progressed after treatment with definitive chemo-radiation, or
 - metastatic NSCLC
- 2.3 The pre-PBAC response provided documentation that indicated the TGA Delegate had requested the following amendments to the proposed indication following the ACM meeting: “[cemiplimab] as monotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 [TPS $\geq 50\%$] as determined by a validated test, with no EGFR, ALK or ROS1 aberrations, who have:
- locally advanced NSCLC who are not candidates for definitive chemoradiation, or
 - metastatic NSCLC”.

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	No. of Rpts	Dispensed price for maximum amount	Proprietary Name, and Manufacturer
CEMIPLIMAB 350 mg/7 mL injection, 10 mL vial solution for infusion, 1 x 10 mL vial	350 mg	6	Published \$7,729.71 – Public ^a \$7,877.36 – Private ^a Effective: TBD	Libtayo®, sanofi-aventis Australia Pty Ltd

TBD = to be determined

^a The published price would be \$7,730.21 in a public hospital setting and \$7,878.26 in a private hospital setting, based on the Efficient Funding of Chemotherapy (EFC) mark-ups and fees as of 1st July 2021 and an ex-manufacturer price of \$7,643.93 per 350 mg vial.

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Category / Program:	Section 100 – Efficient Funding of Chemotherapy Chemotherapy Items for Public Hospital Use Chemotherapy Items for Private Hospital Use
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IV (metastatic)
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) NSCLC
Treatment phase:	Initial treatment – 3 weekly treatment regimen
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<ul style="list-style-type: none"> • 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 express programmed cell death ligand 1 (PD-L1) with a tumour score of at least 50% in the tumour sample, 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 • <i>The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition AND</i> • The treatment must not exceed a total of 7 doses under this restriction. <p><u>Note</u> 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.</p> <p><u>Note</u> A patient may only qualify for PBS-subsidised treatment under this restriction once.</p> <p><u>Note</u> Following completion of the initial PBS subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.</p>
Population criteria	<ul style="list-style-type: none"> • <i>Patient must be aged 18 years or older.</i>

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CEMIPLIMAB 350 mg/7 mL injection, 10 mL vial solution for infusion, 1 x 10 mL vial	350 mg	6	Libtayo®	sanofi-aventis Australia Pty Ltd

Category / Program:	Section 100 – Efficient Funding of Chemotherapy Chemotherapy Items for Public Hospital Use Chemotherapy Items for Private Hospital Use
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IV (metastatic)
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) NSCLC
Treatment phase:	Continuing treatment – 3 weekly treatment regimen
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<ul style="list-style-type: none"> • Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND • Patient must not have developed disease progression while being treated with this drug for this condition, AND • <i>The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition, AND</i> • The treatment must not exceed a total of 35 cycles or up to 24 months of <i>treatment under both initial and continuing treatment restrictions under this restriction.</i>

3.2 The submission stated that the sponsor would seek a Special Pricing Arrangement (SPA). Published prices for cemiplimab were calculated on a cost-minimisation basis versus pembrolizumab, using the PBS-listed price for pembrolizumab. As the effective price for pembrolizumab is confidential, the submission stated that the effective price for cemiplimab is to be determined after a positive recommendation.

3.3 Overall, the wording of the proposed PBS restriction for cemiplimab was similar to that of pembrolizumab, except that the proposed listing of cemiplimab included a criterion regarding the level of PD-L1 expression (i.e. TPS \geq 50%). Initially, pembrolizumab was listed on the PBS, as monotherapy, for treatment of NSCLC patients with high expression of PD-L1 (i.e. TPS \geq 50%). Subsequently, pembrolizumab, in combination with chemotherapy, received a positive PBAC recommendation for treatment of NSCLC, regardless of PD-L1 expression. The current PBS restriction for pembrolizumab does not include a criterion on PD-L1 expression level, as the PBAC decided to consolidate its listing to allow clinicians to determine whether in combination with chemotherapy or as monotherapy is used according to its approved

TGA indications (Broad PBS subsidy listing for PD-(L)1 checkpoint inhibitors for NSCLC Public Summary Document (PSD), August 2019 PBAC meeting).

- 3.4 The proposed PBS population is broader than the patient population in the key clinical evidence for cemiplimab (Study 1624) by not precluding use never smokers, but narrower than the Study 1624 population and the proposed TGA indication by limiting the use of cemiplimab in metastatic NSCLCs (not for locally advanced disease). The ESC noted that Study 1624 excluded never smokers, however considered that a criterion related to smoking history was not required in the proposed PBS listing.
- 3.5 The proposed PBS listing does not preclude the use cemiplimab in combination with other therapies, e.g. chemotherapy. The Pre-Sub-Committee Response (PSCR) agreed with the suggestion by the Secretariat to add a restriction to limit the use of cemiplimab to monotherapy if considered necessary by the PBAC. The ESC considered that as the submission only provided evidence on the use of cemiplimab as monotherapy for treatment of PD-L1 TPS \geq 50% NSCLC, an additional restriction to limit the use of cemiplimab to monotherapy was appropriate.
- 3.6 The pre-PBAC response requested two changes to the proposed initial treatment restriction. Specifically, the sponsor requested to remove the following notes: “A patient may only qualify for PBS subsidised treatment under this restriction once.”; and “Following completion of the initial PBS subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.”
- 3.7 The PBAC considered it would appropriate to include reference to ‘tumour proportion score (TPS)’ in the clinical criteria, rather ‘tumour score’, to more accurately reflect the proposed TGA indication.
- 3.8 This application is being considered under the streamlined codependent submission process. To be eligible for cemiplimab treatment, patients need to be tested for PD-L1 expression. Currently an immunohistochemical (IHC) test is listed on the MBS to determine if the requirements relating to the PD-L1 status for access to pembrolizumab under the PBS are fulfilled (MBS item 72814). A concurrent minor submission was lodged to MSAC, to request amendment to the MBS item 72814 to include cemiplimab. The proposed wording for MBS item descriptor is presented below.

Table 2: Proposed wording for MBS item descriptor

CATEGORY 6 – PATHOLOGY SERVICES
<p><u>72814</u></p> <p>Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the programmed cell death ligand 1 (PD-L1) antibody of tumour material from a patient diagnosed with non-small cell lung cancer, to determine if the requirements relating to PD-L1 status for access to pembrolizumab or cemiplimab under the Pharmaceutical Benefits Scheme are fulfilled.</p> <p>Fee: \$74.50 Benefit: 75% = \$55.90 85% = \$63.35</p>

Source: Table 1, p1 of the minor MSAC submission.

Note: Proposed changes to the current MBS item descriptor are **bold** and underlined.

- 3.9 The evaluation stated that given PD-L1 testing is likely to be a part of the routine clinical management for NSCLC, the minor revision to MBS item 72814 is not expected to increase the usage of PD-L1 testing in clinical practice. The PBAC confirmed that PD-L1 testing is already part of standard of care in the proposed population and that listing of cemiplimab will not alter that.

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

4 Population and disease

- 4.1 Lung cancer is the leading cause of death and the fifth most common cancer diagnosis in Australia. In Australia in 2011, 42.2% (4,273 out of 10,134) of lung cancers were diagnosed with Stage IV disease, with the disease stage of another 28.5% of diagnoses not recorded. The 5-year survival rate for Stage IV lung cancer was only 3.2% in 2011-2016¹. NSCLC is the most common type of lung cancer and accounts for around 85%-90% of all cases².
- 4.2 The submission proposed cemiplimab to be used as a first-line treatment for patients with Stage IV NSCLC whose tumour has PD-L1 expression in $\geq 50\%$ tumour cells, is EGFR wildtype, and negative for ALK or ROS1 gene rearrangement, and has a performance status of 0 or 1. These patients are currently eligible for PBS-subsidised pembrolizumab monotherapy. Other treatment options are pembrolizumab + chemotherapy, atezolizumab + bevacizumab + chemotherapy (for non-squamous NSCLC) and nivolumab + ipilimumab + chemotherapy (for squamous NSCLC).
- 4.3 Cemiplimab is a fully recombinant human immunoglobulin G4 monoclonal antibody that targets the programmed cell death 1 (PD-1) receptor and is part of the pharmacologic class of PD-1 blocking antibodies. Cemiplimab blocks the interaction of PD-1 with its ligands PD-L1 and PD-L2 which potentiates T-cell responses, including anti-tumour responses.
- 4.4 The recommended dose of cemiplimab is 350 mg administered as an intravenous (IV) infusion over 30 minutes every 3 weeks (Q3W) until disease progression or unacceptable toxicity, for a maximum treatment duration of 24 months.

5 Comparator

- 5.1 The submission nominated pembrolizumab monotherapy as the main comparator. The main arguments provided in support of this nomination were that pembrolizumab is the most prescribed immunotherapy in Australia for patients with Stage IV NSCLC with high expression of PD-L1 (i.e. TPS $\geq 50\%$) and that pembrolizumab is the only immunotherapy that can be used as monotherapy for the proposed PBS population.

¹ Australian Institute of Health and Welfare (AIHW). Cancer data in Australia. Cat. no: CAN 122. AIHW. 2021; Available from: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/summary>.

² Cancer Australia. Lung cancer: Types of lung cancer. Cancer Australia, Australian Government. 2020; Available from: <https://www.canceraustralia.gov.au/affected-cancer/cancer-types/lung-cancer/types-lung-cancer>.

The ESC noted that some patients within the proposed PBS population (i.e. TPS \geq 50%) may be treated with pembrolizumab in combination with chemotherapy instead of pembrolizumab monotherapy, but considered that pembrolizumab monotherapy remained the appropriate comparator for cemiplimab monotherapy.

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 individuals (2) and organisations (4) via the Consumer Comments facility on the PBS website. The comments from individuals described the experience of patients who had used this medicine and spoke positively of its effectiveness, prolonging length and quality of life.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the cemiplimab submission on the basis of the EMPOWER-Lung 1 study (referred to as Study 1624 in this submission). The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for cemiplimab, of 5 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)³, based on a comparison with chemotherapy, while also noting that pembrolizumab is the PBS comparator.

6.4 The PBAC noted the advice from Lung Foundation Australia, in particular that cemiplimab would provide clinicians and patients with an additional choice of treatment and secure an alternative line of supply for continued access to treatment for patients with late stage NSCLC.

6.5 The PBAC noted the advice from the Centre for Community-Driven Research which described the results of a patient survey based on a number of telephone interviews conducted in 2018. The survey enrolled participants from all stages of lung cancer, with half of all participants having stage IV lung cancer. The PBAC noted key themes arising from the survey included the importance of rapid access to new treatments, desire for targeted treatments with limited toxicity, psychosocial impact of cancer diagnosis, and lung cancer stigma. The PBAC noted that the survey was not specific to cemiplimab, but was a generic survey which helped provide some key themes of importance to people with stage IV lung cancer

6.6 The PBAC noted the advice from Rare Cancers Australia, which supported the listing of cemiplimab, as an alternative checkpoint inhibitor for NSCLC patients with significant PD-L1 expression.

³ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Clinical studies

- 6.7 The submission was based on an indirect treatment comparison (ITC) of:
- One cemiplimab trial, Study 1624, which compared cemiplimab monotherapy with platinum-based chemotherapy for first-line treatment of patients with locally advanced or metastatic NSCLC whose tumour expressed PD-L1 TPS $\geq 50\%$ and was EGFR wildtype, ALK translocation negative and ROS1 gene rearrangement negative; and
 - Two pembrolizumab trials, KN024 and KN042, which compared pembrolizumab monotherapy with platinum-based chemotherapy as first-line treatment of NSCLC patients. KN024 only included metastatic NSCLC patients with PD-L1 TPS $\geq 50\%$ and with no EGFR or ALK genomic tumour aberrations. KN042 had broader inclusion criteria, as it recruited patients with locally advanced or metastatic disease and used a lower threshold for PD-L1 expression of TPS $\geq 1\%$. The level of PD-L1 expression (TPS of 1-49% vs. $\geq 50\%$) was a stratification factor in KN042.
- 6.8 The two pembrolizumab trials, KN024 and KN042, have previously been reviewed by the PBAC in the submissions of pembrolizumab monotherapy for first-line treatment of Stage IV, PD-L1 TPS $\geq 50\%$ NSCLC (KN024, as the intervention trial) (pembrolizumab PSDs, March 2017 and November 2017 PBAC meetings) and the submissions of pembrolizumab + chemotherapy combination therapy for first-line treatment of Stage IV NSCLC, regardless of PD-L1 expression level (KN024 and KN042, as the comparator trials) (pembrolizumab PSDs, November 2018 and July 2019 PBAC meetings).
- 6.9 The submission also presented results from a recently published KN042 China Study as supplementary evidence. This study included patients enrolled from mainland China in the KN042 global study and in the KN042 China extension study. A total of 92 out of 262 (35%) patients in the KN042 China Study were also included in the main KN042 study, with the remaining 170 Chinese subjects recruited after global enrolment was completed. Given the overlap of the trial populations between KN042 and KN042 China Study, it appeared reasonable not to include KN042 China Study in the ITC.
- 6.10 Details of the trials presented in the submission are provided in the table below.

Table 3: Studies and associated reports presented in the submission

Trial ID	Protocol title / Publication title	Publication citation
Cemiplimab trials		
Study 1624 EMPOWER-Lung 1	<p>A global, randomized, Phase 3, open-label study of REGN2810 (anti-PD-1 antibody) versus platinum-based chemotherapy in first-line treatment of patients with advanced or metastatic PD-L1 + non-small cell lung cancer.</p> <p>A global, randomized, Phase 3, open label study of REGN2810 (anti-PD-1 antibody) versus platinum based chemotherapy in first line treatment of patients with advanced or metastatic PD L1 + non-small cell lung cancer. Protocol Amendment 7.</p> <p>Sezer A, Kilickap S, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial.</p> <p>Gumus M, Chen C-I, et al. Patient-reported symptoms, functioning, and quality of life (QoL) in patients treated with cemiplimab monotherapy for first-line treatment of advanced NSCLC with PD-L1 \geq 50%: Results from EMPOWER-Lung 1 study. (Abstract)</p>	<p>August 2020</p> <p>May 2019</p> <p>Lancet 2021; 397: 592-604.</p> <p>Journal of Clinical Oncology 39(15_suppl.): 9078.</p>
Pembrolizumab trials		
KN024	<p>Reck M, Rodrigues-Abreu D, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small cell lung cancer with PD-L1 Tumor Proportion Score \geq50%.</p> <p>Satouchi M, Nosaki K, et al. First-line pembrolizumab vs chemotherapy in metastatic non-small-cell lung cancer: KEYNOTE-024 Japan subset.</p> <p>Reck M, Rodrigues-Abreu D, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 Tumor Proportion Score of 50% or greater.</p> <p>Brahmer JR, Rodrigues-Abreu D, et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial.</p> <p>Reck M, Rodrigues-Abreu D, et al. 2016. Pembrolizumab versus chemotherapy for PD-L1–positive non-small-cell lung cancer.</p> <p>Brahmer J, Rodrigues-Abreu D, et al. Updated analysis of KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy for advanced NSCLC with PD-L1 TPS \geq50%. (Abstract OA 17.06)</p> <p>Brahmer J, Rodrigues-Abreu D, et al. Progression after the next line of therapy (PFS2) and updated OS among patients (pts) with advanced NSCLC and PD-L1 tumor proportion score (TPS) \geq50% enrolled in KEYNOTE 024. (Abstract)</p>	<p>Journal of Clinical Oncology 2021; 39(21): 2339-49</p> <p>Cancer Science 2020; 111(12):4480-9.</p> <p>Journal of Clinical Oncology 2019; 37(7): 537-46.</p> <p>The Lancet Oncology 2017; 18(12): 1600-9.</p> <p>New England Journal of Medicine 2016; 375(19): 1823-33.</p> <p>Journal of Thoracic Oncology 2017; 23 (11 suppl. 2): S1793-4.</p> <p>Journal of Clinical Oncology 2017; 35(5 suppl.): 9000.</p>
KN042	<p>Mok TSK, Wu YL, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial.</p> <p>Mok TSK, Wu YL, et al. 2019b. Final analysis of the phase III KEYNOTE-042 study: Pembrolizumab versus platinum-based chemotherapy as first-line therapy for patients with PD-L1–positive locally advanced/metastatic NSCLC. (Abstract 1020)</p>	<p>Lancet 2019; 393(10183): 1819-30.</p> <p>Annals of Oncology 2019; 30(suppl. 2): ii3819.</p>

Trial ID	Protocol title / Publication title	Publication citation
KN042 China Study (supplementary evidence)	Wu YL, Zhang L, et al. Randomized clinical trial of pembrolizumab vs chemotherapy for previously untreated Chinese patients with PD-L1-positive locally advanced or metastatic non-small-cell lung cancer: KEYNOTE-042 China Study. Wu YL et al. 2020. Updated analysis from the KEYNOTE-042 China study: 1L pembrolizumab vs. chemotherapy in Chinese patients with advanced NSCLC with PD-L1 TPS \geq 1%. (Abstract 389P)	International Journal of Cancer 2021; 148(9): 2313-20. Annals of Oncology 2021; 31(suppl. 6): S1394.

Source: Tables 2.2-1 to 2.2-3, pp11-14 of the submission.

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

Table 4: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Patient population	Outcomes
Cemiplimab vs. platinum-based chemotherapy				
Study 1624	710	R, OL, MC 13.1 mths	Squamous or non-squamous NSCLC patients with locally advanced or metastatic disease. 79% of the ITT population had PD-L1 TPS \geq 50%.	OS, PFS, ORR and AEs
Pembrolizumab vs. platinum-based chemotherapy				
KN024	305	R, OL, MC 11.2-59.9 mths ^a	Squamous or non-squamous NSCLC patients with metastatic disease and PD-L1 TPS \geq 50%	OS, PFS, ORR and AEs
KN042	599 ^b	R, OL, MC 12.8 mths ^c	Squamous or non-squamous NSCLC patients with locally advanced or metastatic disease and PD-L1 TPS \geq 1% (subgroup of patients with PD-L1 TPS \geq 50% was used in the ITC)	OS, PFS, ORR and AEs
Meta-analysis	904	Including KN024 ITT patients and KN042 PD-L1 TPS \geq 50% subgroup for assessment of OS, PFS and AEs ^d		

Source: Compiled during the evaluation based on Sections 2.3 and 2.4 of the submission.

AE = adverse events; ITC = indirect treatment comparison; ITT= intention-to-treat; MC = multi-centre; NSCLC = non-small cell lung cancer; PD-L1 TPS = programmed cell death ligand 1 tumour proportion score; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R = randomised.

^a Median duration of follow-up at different data cutoff (DOC) date: DCO May 2016: 11.2 mths, DCO July 2017: 25.2 mths; DCO June 2020: 59.9 mths. Data on PFS and safety at DCO May 2016 and other outcomes (including OS) at DCO July 2017 were used in the indirect comparison.

^b Number of patients in the subgroup of PD-L1 TPS \geq 50%. N = 1,274 for the ITT population.

^c Median duration of follow-up in the ITT population. Relevant data on the PD-L1 TPS \geq 50% subgroup was not available.

^d Meta-analysis of AEs included all subjects as treated from KN024 and KN042.

6.12 In Study 1624, to confirm patient eligibility during the screening period, a central commercial laboratory was used to analyse PD-L1 expression (IHC 22C3 pharmDx assay). During the course of the study, the sponsor became aware that the PD-L1 testing of samples from Study 1624 at the central commercial laboratory had a number of quality issues. After August 2018, patients were tested using the same assay (IHC 22C3 assay) but with additional oversight to ensure that the testing at the commercial laboratory was conducted in accordance with the FDA-approved labelling. Patients who were tested before August 2018 could be retested using the samples from Study 1624 (for those patient samples were still available). There were three populations for assessment of efficacy data:

- Full Analysis population (i.e. all randomised patients – intention-to-treat (ITT) population) (N=710).

- Modified ITT 1 (mITT-1) population (N=563): All randomised patients who were enrolled based on tests performed after August 2018 (n=475), as well as patients whose PD-L1 samples tested before August 2018 and required retesting, and upon retest, were confirmed as having PD-L1 TPS $\geq 50\%$ (n=88).
 - Modified ITT 2 (mITT-2) population (N=475): All randomised patients who were tested after August 2018 with PD-L1 TPS of $\geq 50\%$.
- 6.13 The primary ITC for efficacy was based the Study 1624 ITT population versus the meta-analysis of the KN024 ITT population and the KN042 pre-specified subgroup with PD-L1 TPS $\geq 50\%$. The other two populations from Study 1624, i.e. mITT-1 and mITT-2, were used in the sensitivity analyses. All subjects as treated from Study 1624, KN024 and KN042 were involved in the ITC of safety outcomes.
- 6.14 The ITC was performed using the Bucher (1997) method⁴, via platinum doublet as the common reference. The submission claimed that the nominated non-inferiority margin for overall survival (OS) was based on previous PBAC consideration of atezolizumab as a later-line therapy for locally advanced or metastatic NSCLC (atezolizumab PSD, November 2017 PBAC meeting). It was noted that the nominated non-inferiority criteria, i.e. OS hazard ratio 1.04 (95%CI: 0.70, 1.54), as mentioned in the atezolizumab submission was from a comparison of nivolumab versus pembrolizumab for melanoma, which may not be applicable to the proposed NSCLC indication. This non-inferiority threshold was mentioned in the atezolizumab PSD. However, the PBAC's acceptance of non-inferiority of atezolizumab versus nivolumab was based on the additional scenario analyses provided in the Pre-Sub-Committee Response, not the comparison quoted. The proposed non-inferiority threshold has not been previously accepted by the PBAC and it was not adequately justified in the submission.
- 6.15 The results of the indirect comparison were subject to high risk of bias, given the indirect nature of the comparison and the transitivity concerns across the trials included in the indirect comparison. These will be discussed further below.
- 6.16 Given the open-label design of the cemiplimab and pembrolizumab trials, patients and investigators were not blinded to treatment allocation. In each of the individual trials, there is a high risk of bias for the patient-reported outcomes, such as incidence and severity of adverse events (AEs). Since disease progression was assessed by an Independent Review Committee (IRC) that was blinded to treatment assignment, there was a low risk of bias for assessment of outcomes associated with treatment response, e.g. progression-free survival (PFS) and objective response rate (ORR).

Comparative effectiveness

- 6.17 The OS and PFS results for the ITT population in Study 1624 are presented below.

⁴ Bucher HC, Guyatt GH, *et al.* The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of clinical epidemiology*. 1997;50(6):683-91.

Table 5: Results of OS and PFS per IRC – primary analysis in Study 1624 ITT population

	Cemiplimab (N=356)	Chemotherapy (N=354)
OS		
Number of deaths, n (%)	108 (30.3%)	141 (39.8%)
Number of censored patients, n (%)	248 (69.7%)	213 (60.2%)
Median [95% CI], months ^a	22.1 [17.7, NE]	14.3 [11.7, 19.2]
Stratified log-rank test p-value ^{b, c}	0.0022	
HR [95% CI] ^{b, d}	0.676 [0.525, 0.870]	
Estimated survival probability, % [95% CI] ^a		
6 months	81.2 [76.4, 85.1]	76.2 [71.0, 80.6]
12 months	70.3 [64.4, 75.4]	55.7 [49.2, 61.7]
18 months	56.1 [48.1, 63.3]	43.3 [35.8, 50.4]
24 months	48.6 [39.2, 57.3]	29.7 [18.8, 41.4]
PFS per IRC		
Number of events, n (%)	201 (56.5%)	262 (74.0%)
Progressive disease, n (%)	158 (44.4%)	203 (57.3%)
Deaths, n (%)	43 (12.1%)	59 (16.7%)
Number of censored patients, n (%)	155 (43.5%)	92 (26.0%)
Median [95% CI], months ^a	6.2 [4.5, 8.3]	5.6 [4.5, 6.1]
Stratified log-rank test p-value ^{b, c}	<0.0001	
HR [95% CI] ^{b, d}	0.593 [0.491, 0.718]	
Estimated event-free probability, % [95% CI] ^a		
6 months	53.1 [47.4, 58.5]	48.0 [42.2, 53.6]
12 months	37.8 [31.9, 43.6]	7.2 [4.3, 11.2]

Source: Table 2.5-1, p52 of the submission

CI = confidence interval; HR = hazard ratio; IRC = Independent Review Committee; ITT = intention-to-treat; IWRS = Interactive Web Response System; NE = not evaluable; OS = overall survival; PFS = progression-free survival

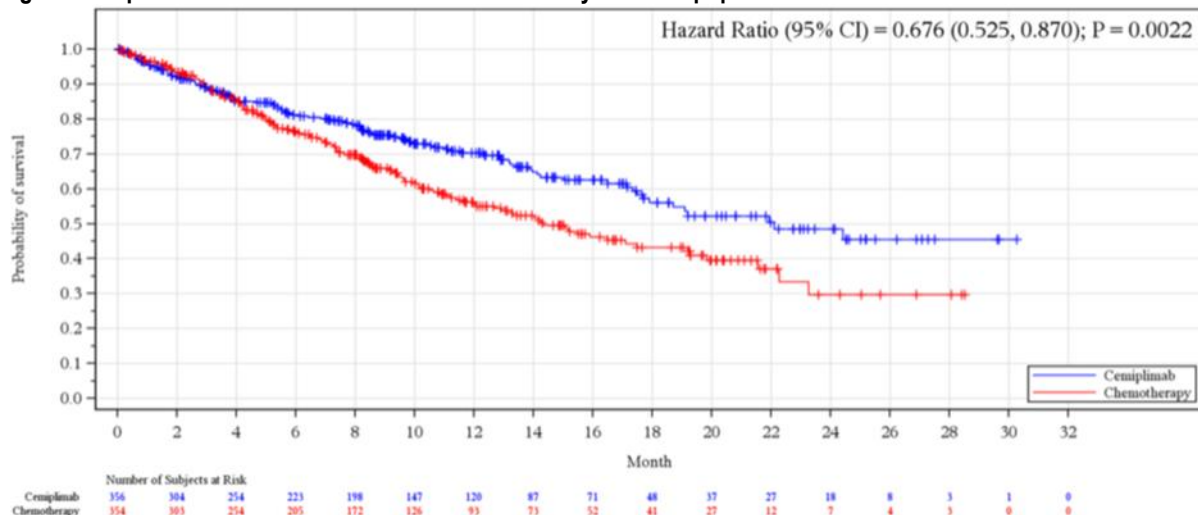
^a Based on Kaplan-Meier method.

^b Stratified by histology (squamous vs. non-squamous) according to IWRS.

^c Two-sided p-value. Significance threshold for OS was set to 0.0025 using the O'Brien Fleming alpha spending function.

^d Based on stratified proportional hazards model (cemiplimab vs. chemotherapy).

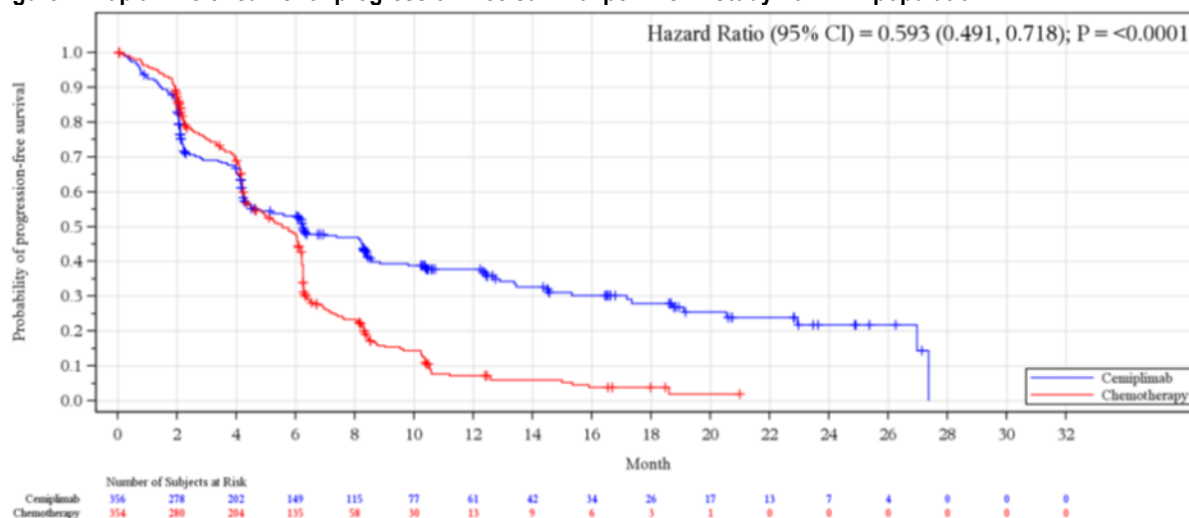
Figure 1: Kaplan-Meier curve for overall survival in Study 1624 ITT population



Source: Figure 2.5-1, p53 of the submission

CI = confidence interval; ITT = intention-to-treat

Figure 2: Kaplan-Meier curve for progression-free survival per IRC in Study 1624 ITT population



Source: Figure 2.5-4, p56 of the submission

CI = confidence interval; IRC = Independent Review Committee; ITT = intention-to-treat

- 6.18 With a median follow-up of 13.1 months, the median OS in the cemiplimab monotherapy arm of the ITT population was 7.8 months longer than that in the platinum-based chemotherapy arm (22.1 months versus 14.3 months); and the difference was statistically significant (hazard ratio: 0.68 [95% CI: 0.53, 0.87]). The Kaplan-Meier estimates of OS at 12 months was 70.3% in patients receiving cemiplimab, compared with 55.7% in the comparator arm; and the OS estimates at 24 months in the two treatment arms were 48.6% and 29.7%, respectively.
- 6.19 Statistically significant OS benefit of cemiplimab was also observed in the mITT-1 population (N=563) and mITT-2 population (N=475). The point estimates of OS hazard ratio in mITT-1 and mITT-2 patients were both lower (more relative benefits of cemiplimab vs. chemotherapy) compared with the hazard ratio estimate in the ITT population (0.57 [0.42, 0.77] in mITT-1 and 0.57 [0.40, 0.80] in mITT-2 vs. 0.68 [0.53, 0.87] in ITT).
- 6.20 Similar to OS, ITT patients who were treated with cemiplimab monotherapy demonstrated statistically significantly greater PFS compared to those receiving platinum doublet (median: 6.2 months vs. 5.6 months), with a hazard ratio of 0.59 [0.49, 0.72]. The Kaplan-Meier estimate of PFS at 12 months was 30.6 percentage points higher in the cemiplimab group than in the chemotherapy group (37.8% vs. 7.2%).
- 6.21 The PFS hazard ratio in mITT-1 patients was slightly lower (more relative benefits of cemiplimab vs. chemotherapy) than the ITT hazard ratio (0.54 [0.43, 0.68] vs. 0.59 [0.49, 0.72]). The PFS results in the mITT-2 patients were similar to the ITT results in terms of both median PFS (6.3 months for cemiplimab and 5.6 months for chemotherapy vs. 6.2 months for cemiplimab and 5.6 months for chemotherapy) and hazard ratio (0.60 [0.47, 0.77] vs. 0.59 [0.49, 0.72]).

- 6.22 Other secondary outcomes of ORR and duration of response in Study 1624 also suggested a superior treatment effect of cemiplimab over platinum doublet in the ITT, mITT-1 and mITT-2 populations.
- 6.23 The following differences between Study 1624 and the Australian setting were identified by the evaluation which could have affected the applicability of the trial results to the proposed PBS population:
- Study 1624 excluded never smokers. Evidence from trials of other PD-(L)1 inhibitors showed no benefit of PD-(L)1 inhibitors for metastatic NSCLC patients with high PD-L1 expression (TPS \geq 50%) in the subgroup of never smokers⁵. However, the interaction between smoking status and cemiplimab cannot be assessed as never smokers were not included in Study 1624. The PBAC noted the exclusion of never smokers enriched the population of patients with squamous NSCLC (see next point). The PBAC acknowledged the PSCR statement that never smokers are less likely to present with high PD-L1 expression;
 - In Study 1624, 44% of ITT patients had NSCLC of squamous histology. This proportion was higher than the estimate (26%) noted in the nivolumab Drug Utilisation Sub-Committee (DUSC) report (2020)⁶. Subgroup analysis suggested a trend of more benefits from cemiplimab relative to chemotherapy in the squamous subgroup than in the non-squamous subgroup (OS hazard ratio: 0.53 [0.36, 0.77] vs. 0.83 [0.59, 1.16]). Therefore, the overrepresentation of squamous NSCLC patients in Study 1624 could have biased the results in favour of cemiplimab;
 - Study 1624 included subjects with locally advanced NSCLC, who were not included in the proposed PBS population. This, however, is unlikely to greatly affect the applicability of the trial results to the target population, given the small number of patients with locally advanced disease in Study 1624 (16%) and the similar results between the Stage IV subgroup and the overall ITT population; and
 - Patients in the cemiplimab arm of Study 1624 were allowed to continue cemiplimab after progression for up to 108 weeks, with the addition of histology-specific platinum-based doublet chemotherapy for four cycles. Of 71 (45% of progressors, 20% of ITT) patients who received subsequent anti-cancer therapy after disease progression in the cemiplimab arm, 51 patients (32% of progressors, 14% of ITT) were treated with cemiplimab + chemotherapy as extended treatment. Benefits of continuation of cemiplimab therapy after progression, with addition of chemotherapy, hasn't been previously established. Nevertheless, a potential confounding effect on OS (potential inflation of the OS effect) cannot be

⁵ Dai L, Jin B, Liu T, *et al.* The effect of smoking status on efficacy of immune checkpoint inhibitors in metastatic non-small cell lung cancer: A systematic review and meta-analysis. *EClinicalMedicine*. 2021;38:100990.

⁶ Drug Utilisation Sub-Committee (DUSC). Nivolumab for the treatment of non-small cell lung cancer: 24 month predicted versus actual analysis. 2020. Canberra.

ruled out, as such use is not allowed by the proposed PBS listing or Product information.

- 6.24 The ESC noted the differences between Study 1624 and the Australian setting (see paragraph 6.23) but considered that, overall, the evidence is reasonably applicable to the Australian setting.
- 6.25 Data on KN024 and KN042 were available at different data cutoff (DCO) dates. Results from KN024 at DCO May 2016 (for PFS) and DCO July 2017 (for OS and ORR) and from KN042 at DCO February 2018 were used in the ITC due to the duration of follow-up being similar to Study 1624. The submission also presented updated data for KN024 (DCO June 2020) and KN042 (DCO September 2018), and the results from KN042 China Study. In summary, the updated data from KN024 and KN042 and the results of KN042 China Study were largely consistent with the results used in the ITC.
- 6.26 The primary ITC results of OS and PFS are presented below.

Table 6: Summary of results of the indirect comparison for OS and PFS

	Trial ID	Follow-up, mths	N	PD-1 inhibitor Median, mths [95% CI]	N	Chemotherapy Median, mths [95% CI]	HR [95% CI]
OS							
Cemiplimab vs. chemotherapy	1624 ITT	13.1	356	22.1 [17.7, NE]	354	14.3 [11.7, 19.2]	0.68 [0.53, 0.87]
	1624 mITT-1	13.1	283	NR [17.9, NE]	280	14.2 [11.2, 17.5]	0.57 (0.42, 0.77)
Pembrolizumab vs. chemotherapy	KN024 ITT	25.2 ^a	154	30.0 [18.3, NR]	151	14.2 [9.8, 19.0]	0.63 [0.47, 0.86]
	KN042 ≥ 50% TPS	12.8	299	20.0 [15.4, 24.9]	300	12.2 [10.4, 14.2]	0.69 [0.56, 0.85]
	KN meta-analysis k = 2 ^b			–			0.67 [0.56, 0.80]
ITC of cemiplimab vs. pembrolizumab	1624 ITT vs. KN meta-analysis			–			1.01 [0.74, 1.37]
	1624 mITT-1 vs. KN meta-analysis			–			0.84 [0.59, 1.20]
PFS							
Cemiplimab vs. chemotherapy	1624 ITT	13.1	356	6.2 [4.5, 8.3]	354	5.6 [4.5, 6.1]	0.59 [0.49, 0.72]
Pembrolizumab vs. chemotherapy	KN024 ITT	11.2 ^c	154	10.3 [6.7, NR]	151	6.0 [4.2, 6.2]	0.50 [0.37, 0.68]
	KN042 ≥ 50% TPS	12.8	299	7.1 [5.9, 9.0]	300	6.4 [6.1, 6.9]	0.81 [0.67, 0.99]
	KN meta-analysis k = 2 ^d			–			0.65 [0.40, 1.04]
ITC of cemiplimab vs. pembrolizumab	1624 ITT vs. KN meta-analysis			–			0.91 [0.55, 1.53]

Source: Table 2.6-16, p102 and Table 2.6-3, p90 of the submission; “2021-07-05_MA&ITC” Excel workbook for indirect comparison
 CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; ITT = intention-to-treat; k = number of studies contributing to the pooled estimate of effect; mths = months; mITT-1 = modified intention to treat population 1; NE = not evaluable; NR = not reached; PD-1 = programmed cell death 1; TPS = tumour proportion score.

Notes: A HR <1 in ITC favours cemiplimab. Results of the primary ITCs are shaded.

^a Overall survival data at data cutoff (DCO) July 2017 in KN024, as median overall survival were not reached at an earlier DCO of May 2016.

^b Random-effect model. Heterogeneity: Tau²=0.00; Chi²=0.24, df=1, P=0.63; I²=0%

^c Progression-free survival data at DCO May 2016 in KN024

^d Random-effect model. Heterogeneity: Tau²=0.10; Chi²=6.84, df=1, P=0.009; I²=85%

6.27 The point estimate of indirect hazard ratio for OS for the primary comparison suggested no significant difference in the treatment effect of cemiplimab versus chemotherapy compared with pembrolizumab versus chemotherapy (indirect hazard ratio: 1.01 [0.74, 1.37]). The 95% CI contained an increase of hazard for death by 37%, which could be clinically important to the proposed target population. Similar results were reported when the ITC used the OS data at an earlier DCO of May 2016 in KN024, and when the mITT-1 and mITT-2 populations of Study 1624 were used.

6.28 There was no significant difference in effect size of cemiplimab and pembrolizumab relative to chemotherapy in term of PFS (hazard ratio: 0.91 [0.55, 1.53]) in the primary ITC. Similar results were reported from sensitivity analyses where mITT-1 and mITT-2 from Study 1624 were used.

6.29 The key differences in the baseline characteristics and treatments across the cemiplimab trial (Study 1624) and the two pembrolizumab trials (KN024 and KN042 (PD-L1 TPS \geq 50% subgroup)) are summarised as follows:

- KN024 enrolled patients with metastatic NSCLC only; whereas Study 1624 and KN042 included both metastatic and locally advanced subjects (16% in Study 1624 and 11% in KN042).
- There were more patients with squamous NSCLC (44%) in Study 1624 than in KN024 (18%) and KN042 (37%).
- Study 1624 had more male patients (85%) compared with KN024 (61%) and KN042 (70%).
- The proportion of patients with brain metastases was higher in Study 1624 (12%) than in KN024 (9%) and KN042 (6%).
- Never smokers were excluded from Study 1624 but included in the two pembrolizumab trials (3% in the pembrolizumab vs. 13% in the chemotherapy arm in KN024 and 22% across both arms in KN042).
- Study 1624 included more patients from Europe (78%) compared with KN024 (52%) or KN042 (23%). A lower proportion of patients were enrolled from Asia in Study 1624 (11%) than in KN042 (31% East Asia⁷).
- The proportion of patients receiving later-line PD-(L)1 inhibitors following first-line chemotherapy was higher in Study 1624 and KN024 (43% and 44% respectively) than in the KN042 ITT population (20%)⁸.
- Around one-third (32%) of patients who had progressive disease after first-line cemiplimab were treated with cemiplimab in combination with chemotherapy in Study 1624; but relevant data on use of pembrolizumab, as continued treatment or as retreatment, in patients who had disease progression in pembrolizumab trials were not available.

6.30 The above heterogeneities across the trials affected the transitivity assumption underpinning the ITC between cemiplimab and pembrolizumab. The higher proportions of males and patients with squamous histology in the cemiplimab Study 1624 could have biased the ITC results in favour of cemiplimab, while the ESC noted some differences may bias against cemiplimab. The effects of the different distribution of smoking history and geographic region, as well as the incomparable extent of use of PD-(L)1 inhibitor after disease progression in both treatment arms across cemiplimab and pembrolizumab trials cannot be reliably determined, given the

⁷ Proportion of subjects in KN042 who were enrolled from Asia was not reported, but should be \geq 31% (for East Asia).

⁸ Relevant data in the PD-L1 TPS \geq 50% were not available.

inconsistency in the results of subgroup analyses across the PD-1 inhibitor trials or the absence of evidence on the treatment effect of PD-1 agents in subgroups of interest.

Comparative harms

6.31 The results of ITC for safety outcomes are presented below.

Table 7: Summary of results of the indirect comparison of safety outcomes

	Trial ID	PD-1 inhibitor n/N (%)	Chemotherapy n/N (%)	RR [95%CI]	OR [95%CI]	RD [95%CI]
Treatment-related adverse events						
Cemiplimab vs. chemotherapy	1624	204/355 (57.5%)	303/342 (88.6%)	0.65 [0.59, 0.71]	0.17 [0.12, 0.26]	-0.31 [-0.37, -0.25]
Pembrolizumab vs. chemotherapy	KN024	113/154 (73.4%)	135/150 (90.0%)	0.82 [0.73, 0.91]	0.31 [0.16, 0.58]	-0.17 [-0.25, -0.08]
	KN042	399/636 (62.7%)	553/615 (89.9%)	0.70 [0.65, 0.74]	0.19 [0.14, 0.26]	-0.27 [-0.32, -0.23]
	KN meta-analysis, k = 2	–		0.75 [0.64, 0.87]	0.22 [0.14, 0.34]	-0.23 [-0.33, -0.12]
ITC cemiplimab vs. pembrolizumab	1624 vs. KN meta-analysis	–		0.86 [0.72, 1.04]	0.79 [0.44, 1.43]	-0.08 [-0.20, 0.04]
Grade 3-5 treatment-related adverse events						
Cemiplimab vs. chemotherapy	1624	50/355 (14.1%)	134/342 (39.2%)	0.36 [0.27, 0.48]	0.25 [0.18, 0.37]	-0.25 [-0.31, -0.19]
Pembrolizumab vs. chemotherapy	KN024	41/154 (26.6%)	80/150 (53.3%)	0.50 [0.37, 0.68]	0.32 [0.20, 0.51]	-0.27 [-0.37, -0.16]
	KN042	113/636 (17.8%)	252/615 (41.0%)	0.43 [0.36, 0.53]	0.31 [0.24, 0.40]	-0.23 [-0.28, -0.18]
	KN meta-analysis, k = 2	–		0.45 [0.38, 0.53]	0.31 [0.25, 0.39]	-0.24 [-0.28, -0.19]
ITC cemiplimab vs. pembrolizumab	1624 vs. KN meta-analysis	–		0.80 [0.57, 1.11]	0.82 [0.53, 1.26]	-0.01 [-0.09, 0.06]
Treatment-related adverse events leading to treatment discontinuation						
Cemiplimab vs. chemotherapy	1624	18/355 (5.1%)	12/342 (3.5%)	1.45 [0.71, 2.95]	1.47 [0.70, 3.10]	0.02 [-0.01, 0.05]
Pembrolizumab vs. chemotherapy	KN024	11/154 (7.1%)	16/150 (10.7%)	0.67 [0.32, 1.40]	0.64 [0.29, 1.44]	-0.04 [-0.10, 0.03]
	KN042	57/636 (9.0%)	58/615 (9.4%)	0.95 [0.67, 1.35]	0.95 [0.64, 1.39]	0.00 [-0.04, 0.03]
	KN meta-analysis, k = 2	–		0.89 [0.65, 1.22]	0.88 [0.62, 1.24]	-0.01 [-0.04, 0.02]
ITC cemiplimab vs. pembrolizumab	1624 vs. KN meta-analysis	–		1.62 [0.74, 3.55]	1.67 [0.73, 3.80]	0.03 [-0.02, 0.07]
Treatment-related adverse events leading to death						
Cemiplimab vs. chemotherapy	1624	9/355 (2.5%)	7/342 (2.0%)	1.24 [0.47, 3.29]	1.24 [0.46, 3.38]	0.00 [-0.02, -0.03]
Pembrolizumab vs. chemotherapy	KN024	1/154 (0.6%)	3/150 (2.0%)	0.32 [0.03, 3.09]	0.32 [0.03, 3.11]	-0.01 [-0.04, 0.01]
	KN042	13/636 (2.0%)	14/615 (2.3%)	0.90 [0.43, 1.89]	0.90 [0.42, 1.92]	0.00 [-0.02, 0.01]
	KN meta-analysis, k = 2	–		0.81 [0.40, 1.65]	0.81 [0.39, 1.66]	-0.01 [-0.02, 0.01]
ITC cemiplimab vs. pembrolizumab	1624 vs. KN meta-analysis	–		1.53 [0.46, 5.11]	1.54 [0.45, 5.28]	0.01 [-0.01, 0.04]

	Trial ID	PD-1 inhibitor n/N (%)	Chemotherapy n/N (%)	RR [95%CI]	OR [95%CI]	RD [95%CI]
Immune-related adverse events						
Cemiplimab vs. chemotherapy	1624	62/355 (17.5%)	8/342 (2.3%)	7.47 [3.63, 15.36]	8.83 [4.16, 18.76]	0.15 [0.11, 0.19]
Pembrolizumab vs. chemotherapy	KN024	45/154 (29.2%)	7/150 (4.7%)	6.26 [2.92, 13.44]	8.43 [3.66, 19.43]	0.25 [0.17, 0.32]
	KN042	177/636 (27.8%)	44/615 (7.2%)	3.89 [2.85, 5.31]	5.00 [3.52, 7.12]	0.21 [0.17, 0.25]
	KN meta-analysis, k = 2	–		4.32 [2.93, 6.38]	5.63 [3.67, 8.66]	0.21 [0.18, 0.25]
ITC cemiplimab vs. pembrolizumab	1624 vs. KN meta-analysis	–		1.73 [0.76, 3.92]	1.57 [0.66, 3.73]	-0.06 [-0.11, -0.01]
Grade 3-5 immune-related adverse events						
Cemiplimab vs. chemotherapy	1624	13/355 (3.7%)	1/342 (0.3%)	12.52 [1.65, 95.22]	12.96 [1.69, 99.64]	0.03 [0.01, 0.05]
Pembrolizumab vs. chemotherapy	KN024	15/154 (9.7%)	1/150 (0.7%)	14.61 [1.95, 109.23]	16.08 [2.10, 123.34]	0.09 [0.04, 0.14]
	KN042	51/636 (8.0%)	9/615 (1.5%)	5.48 [2.72, 11.03]	5.87 [2.86, 12.03]	0.07 [0.04, 0.09]
	KN meta-analysis, k = 2	–		6.09 [3.15, 11.80]	6.56 [3.33, 12.91]	0.07 [0.05, 0.09]
ITC cemiplimab vs. pembrolizumab	1624 vs. KN meta-analysis	–		2.06 [0.24, 17.36]	1.98 [0.23, 16.95]	-0.04 [-0.06, -0.01]

Source: Table 2.6-20 to Table 2.6-25, pp106-120 of the submission

CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; k = number of studies contributing to the pooled estimate of effect; OR = odds ratio; PD-L1 = programmed cell death ligand 1; RD = risk difference; RR = relative risk;

Notes: ITC for safety used all subjects as treated populations from Study 1624, KN024 and KN042. A RR and OR <1 or RD <0 favours cemiplimab. Results of the primary ITCs are shaded.

6.32 The wide 95% CIs for most of the indirect estimates of treatment effects suggest that the ITC of AEs was statistically underpowered. Clinically meaningful worsening of treatment-related AEs resulting in treatment discontinuation, treatment-related fatal AEs, irAEs (relative measures) and Grade 3-4 irAEs (relative measures), from treatment with cemiplimab compared with pembrolizumab, could not be ruled out based on the 95% CIs from indirect comparisons.

6.33 The type of common AEs reported in Study 1624, e.g. irAEs, anaemia and fatigue in the cemiplimab arm and myelosuppression, nausea and alopecia in the comparator chemotherapy arm, were in line with the known safety profiles of PD-(L)1 agents and platinum-based chemotherapies.

Clinical claim

6.34 The submission described cemiplimab monotherapy as non-inferior to pembrolizumab in terms of effectiveness and safety, based on the ITC presented in the submission. The evaluation identified two key concerns about the evidence supporting the clinical claims:

- There were transitivity issues due to the incomparability of the clinical trials in terms of patient gender, smoking history, region of patient enrolment, NSCLC

histology, brain metastases, switching from first-line chemotherapy to second-line PD-(L)1 inhibitors and continued treatment with PD-(L)1 inhibitors after disease progression. Compared with comparator trials, Study 1624 recruited more males, more patients with squamous histology and more patients with brain metastases. The impacts of the other observed heterogeneities in patient baseline risks and treatments cannot be reliably assessed based on the available evidence.

- The non-inferiority criteria used in the submission, i.e. OS hazard ratio of 1.04 [0.70, 1.54], has not been accepted by the PBAC; nor was it adequately justified in the submission. Clinically meaningful worsening of most of the endpoints assessed, including OS, PFS, treatment-related AEs resulting in treatment discontinuation, treatment-related fatal AEs, irAEs (relative measures) and Grade 3-4 irAEs (relative measures), from treatment with cemiplimab compared with pembrolizumab, could not be ruled out based on the 95% CIs from indirect comparisons.
- 6.35 The ESC considered that the submission's claim that cemiplimab is non-inferior to pembrolizumab in terms of efficacy and safety was likely to be reasonable, in the context of the evidence available. Further discussion is provided below:
- The ESC noted similarities between cemiplimab and pembrolizumab in terms of being within the same therapeutic class, and that the overall design of their respective pivotal studies were similar.
 - With regard to transitivity issues, the ESC noted there were some variations between subjects in Study 1624 (cemiplimab), and KN024 and KN042 (pembrolizumab) trials involved in the indirect comparison as described in paragraph 6.29. The ESC considered these differences might have resulted in heterogeneity of comparative treatment effects of cemiplimab relative to pembrolizumab; but there was potential for bias in both directions, for example smoking status may bias towards cemiplimab but brain metastases may bias towards pembrolizumab. The PBAC noted Study 1624 included a higher proportion of patients with brain metastases (12% vs 9% in KN024, 6% in KN042); however, the PBAC considered the direction of bias was uncertain as this would increase the HR compared to chemotherapy which may bias in favour of cemiplimab but the presence of brain metastases is a poor prognostic factor which may bias against cemiplimab.
 - With regard to the non-inferiority criteria, the ESC considered that the non-inferiority threshold nominated by the submission was not well supported. The ESC also noted that some uncertainty remains due to wide confidence intervals (see Table 6, Table 7).
- 6.36 The PBAC agreed with the ESC and considered that the claim of non-inferior comparative effectiveness and safety was reasonable.

Economic analysis

- 6.37 The submission presented a CMA on the basis of the claimed non-inferiority of cemiplimab to pembrolizumab. The equi-effective doses were estimated as cemiplimab 350 mg Q3W administered as an IV infusion over 30 minutes and pembrolizumab 200 mg Q3W or 400 mg Q6W administered as an IV infusion over 30 minutes, assuming the same treatment durations and dose intensities. In Study 1624, 25.1% of patients had dose delays of cemiplimab. Dosing intensity data were missing from the KN studies. Dose reductions were not allowed in either study. The median treatment durations were similar between cemiplimab (6.8 months in Study 1624) and pembrolizumab (7 months in KN024, 6.6 months in KN042).
- 6.38 As pembrolizumab may be administered in either the 200 mg Q3W dose or 400 mg Q6W dose, whereas cemiplimab must be administered in the 350 mg Q3W dose, pembrolizumab treatments may incur fewer administrations collectively. This was considered in the CMA. The submission used the PBS and RPBS items processed from September 2020 to March 2021 to estimate the proportion of 200 mg vs 400 mg scripts for pembrolizumab, which provided the 94%:6% ratio. As the 200 mg dose is given every 3 weeks, and the 400 mg dose given every 6 weeks, patients who receive the 400 mg dose incur half the IV administration costs of patients receiving 3-weekly dosing. The PBAC considered cemiplimab (given every 3 weeks) was unlikely to substitute for pembrolizumab every 6 weeks to a significant extent.
- 6.39 The results of the CMA are summarised below. The ESC considered that the submission's approach to the CMA was reasonable.

Table 8: Cost minimisation analysis: cemiplimab versus pembrolizumab

Variable	Cemiplimab 350 mg			Pembrolizumab 200 mg			Pembrolizumab 400 mg		
Drug cost (published ex-manufacturer price) per administration									
Dose per administration	350 mg			200 mg			400 mg		
Vials	Unit (mg)	AEMP	# vials	Unit (mg)	AEMP	# vials	Unit (mg)	AEMP	# vials
	350	\$7,643.93	1	100	\$3,823.75	1	100	\$3,823.75	1
List AEMP per administration	350	\$7,643.93	1	200	\$7,647.50	2	400	\$15,295.00	4
Equi-effective dose									
Administrations per Q3W cycle	1			1			0.5		
Equi-effective dose per Q3W cycle	350 mg			200 mg			200 mg		
Drug cost (ex-manufacturer price) per Q3W cycle at equi-effective dose									
Total drug cost per Q3W cycle	\$7,643.93			\$7,647.50			\$7,647.50		
Administration cost									
Number of IV administrations per Q3W cycle	1			1			0.5		
Cost per administration (MBS Item 13950)	\$111.40								
Total administration cost per Q3W cycle	\$111.40			\$111.40			\$55.70		
Total cost (cost-minimisation)									
Total drug and administration cost per Q3W cycle	\$7,755.33			\$7,758.90			\$7,703.20		
Weighted proportion of use of pembrolizumab 200 mg and 400 mg ^a	–			94%			6%		
Weighted price of pembrolizumab across strengths and administration cost	–			\$7,755.33					
Total incremental cost per Q3W cycle (cemiplimab versus pembrolizumab)	\$0.00								

Source: Table 3.4-1, pp 123-124 of the submission.

AEMP = approved ex-manufacturer price; MBS = Medical Benefits Scheme; Q3W = every 3 weeks; Q6W = every 6 weeks.

a. Sourced from Services data from Medicare Australia, from September 2020

- 6.40 An ex-manufacturer price of \$7,643.93 for a 350 mg cemiplimab vial will provide the same cost per administration to pembrolizumab, at its PBS-listed price. The submission calculated the weighted dispensed price for maximum amount (DPMA) as \$7,822.62 using the June 2021 efficient funding of chemotherapy (EFC) mark-ups and fees and a public/private hospital split of 37%/63% (based on the public and private hospitals split of pembrolizumab scripts in the calendar year of 2020).
- 6.41 The submission stated that the PD-L1 test (MBS item 72814) is conducted once for every new patient diagnosed with NSCLC to determine choice of therapy and the PBS listing of cemiplimab is not expected to change clinical practice or increase utilisation of the test. However, given the proposed PBS listing of cemiplimab requires patients to have a PD-L1 TPS \geq 50% and the current PBS listing of pembrolizumab does not specify this requirement, the evaluation considered it may be appropriate to

incorporate the cost of PD-L1 testing into the CMA. This would best be achieved by reducing the cost per patient of cemiplimab by the cost of PD-L1 testing per patient treated with cemiplimab. This is a function of the unit cost of testing and the proportion of those tested who receive cemiplimab, which in turn is a function of those tested with a PD-L1 TPS \geq 50% and, of those, the proportion who do not proceed to cemiplimab treatment for other reasons. The PSCR disagreed with the proposed inclusion of MBS tests in the cost-minimisation analysis, on the grounds that the test would be used for treatment assessment regardless of whether cemiplimab were listed or not. The PSCR indicated that PD-L1 testing is used to guide appropriate usage of all PD-(L)1 inhibitors (pembrolizumab, atezolizumab and nivolumab), as either combination or monotherapy based on PD-L1 expression level (TPS \geq 50% or <50%), despite the revision to the PBS listing for pembrolizumab described above. The PBAC agreed with the ESC that it was reasonable to exclude the costs of PD-L1 testing from the CMA because the test is routinely used in this patient group in clinical practice, to inform the treatment decision for whether the main comparator, pembrolizumab, is used as monotherapy or in combination with chemotherapy. The PBAC considered the listing of cemiplimab for patients with PD-L1 TPS \geq 50% was unlikely to change the utilisation of the test.

- 6.42 The PBAC noted the CMA above was based on the published price of pembrolizumab and the price of cemiplimab would be determined using the effective price of pembrolizumab in this indication.

Drug cost/patient/course

- 6.43 Based on a published DPMA of \$7,826.22, the mean cost per patient is \$85,892. This is based on the mean duration of treatment of 32.94 weeks observed from Study 1624, noting that at the data cut-off of study 1624, 39% of patients were continuing on cemiplimab treatment.

Estimated PBS usage & financial implications

- 6.44 This submission was not considered by DUSC. The submission took a market share approach to estimating the PBS usage of cemiplimab and financial implications. The key inputs for financial estimates are summarised below.

Table 9: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Predicted annual growth rate of pembrolizumab scripts for the treatment of Stage IV NSCLC patients	Pembrolizumab had a rapidly expanding market share, from 2% in 2018 to 51% in 2020. The submission used Excel trendline equations to forecast annual growth rate based on historical Services Australia data for pembrolizumab (November 2018 to March 2021). It calculated that pembrolizumab's annual market growth would be 37% in 2021, and 13% in 2026, based on the linear equations performed in Excel.	Including data when pembrolizumab was first PBS listed may overestimate the market growth rate, as at that time, the usage of first line pembrolizumab was not stable. Pembrolizumab was first listed in Nov 2018 as monotherapy for TPS ≥50% patients only. In July 2019, pembrolizumab was approved for use in all patients, regardless of TPS status. This progression in restrictions opened up pembrolizumab use to a wider target population, which, combined with a shift in treatment preference to first-line immunotherapy, manifest in its rapidly increased market share over this period.
Proportion of Stage IV NSCLC patients with PD-L1 TPS ≥ 50%	13.5%, which is reflective of the weighted proportions of use outlined in Table 2, p4 of the Pembrolizumab NSCLC PSD, July 2019.	The EXPRESS study, a global, multi-centre retrospective observational study of locally advanced and metastatic NSCLC, reported that among 1,064 patients who were negative for both EGFR mutation and ALK alteration, the percentage with PD-L1 TPS ≥ 50% was 27% ⁹ . A sensitivity analysis was performed by the submission, assuming 28.5% of patients would receive pembrolizumab monotherapy.
Market share	█% in Year 1 increasing to █% in Year 6. Based on initial uptake of pembrolizumab in 2018, and the submission's own estimation of uptake.	Uncertain.

Source: Table 4.1-1, pp 125-126 of the submission.

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; MBS = Medicare Benefits Schedule; NSCLC = non-small cell lung cancer; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PD-L1 = programmed death ligand 1; PSD = Public Summary Document; RPBS = Repatriation Pharmaceutical Benefits Scheme; TPS = tumour proportion score.

6.45 The estimated use of cemiplimab and financial implications are summarised below.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	█ ¹	█ ¹	█ ²	█ ²	█ ²	█ ²
Estimated financial implications of cemiplimab						
Cost to PBS/RPBS less copayments	█ ³	█ ³	█ ³	█ ³	█ ⁴	█ ⁴
Estimated financial implications for pembrolizumab						
Cost to PBS/RPBS less copayments	█ ³	█ ³	█ ³	█ ³	█ ⁴	█ ⁴
Net financial implications						
Net cost to PBS/RPBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to MBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to PBS/RPBS/MBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³

⁹ Dietel, M et. al. Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non-small-cell lung cancer: The global, multicenter EXPRESS study. *Lung Cancer*. 2019 Aug;134:174-179.

Source: Table 4.2-10, p133, Table 4.3-5, Table 4.4-1, p136, Tables 4.5-2, and 4.5-3, p137 of the submission.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

6.46 The PBAC considered that the estimated proportion of Stage IV NSCLC patients with PD L1 TPS \geq 50% assumed by the submission (13.5%), may be an underestimate and is likely closer to 30% (see Table 9). The PBAC noted the submission had assumed market share between ■% and ■% over the first six years of listing, which the PBAC considered was a likely overestimate given there are five well-established drugs currently PBS listed for the treatment of NSCLC.

Quality Use of Medicines

6.47 The submission stated that support materials for clinicians and patients will be provided, to explain the benefits and risks associated with cemiplimab treatment for patients with metastatic NSCLC, to help patients better understand their diagnosis, and provide information on treatment with cemiplimab, including potential side effects.

Financial Management – Risk Sharing Arrangements

6.48 The evaluation noted the PBAC may wish to consider whether it would be appropriate for cemiplimab to join the current RSA applying to atezolizumab, durvalumab, ipilimumab, nivolumab and pembrolizumab for the treatment of NSCLC if cemiplimab for the proposed indication is recommended. The PSCR stated the sponsor is amenable to joining the current RSA applying to PD (L)1s for the treatment of NSCLC.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy) Authority Required (Streamlined) listing of cemiplimab for the treatment of previously untreated metastatic non-small cell lung cancer (NSCLC), in patients with a programmed cell death ligand 1 (PD-L1) tumour proportion score (TPS) \geq 50%. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of cemiplimab would be acceptable if it were cost-minimised against pembrolizumab.

7.2 The PBAC did not consider there to be an unmet clinical need for cemiplimab, as there are currently a number of other PBS listed immunotherapies to treat patients with stage IV NSCLC. However, the PBAC noted the consumer comments regarding the value of additional treatment options for patients with NSCLC.

7.3 The PBAC advised that the equi-effective doses are cemiplimab 350 mg Q3W and pembrolizumab 200 mg Q3W. The PBAC noted the CMA presented in the submission was conducted over one 3-week treatment cycle which assumed the same treatment

duration and dose intensity for cemiplimab and pembrolizumab. The PBAC considered this was reasonable given the similar median treatment durations (see paragraph 6.37) and likely similar dose intensities. The PBAC noted pembrolizumab could be administered as 200 mg Q3W or 400 mg Q6W but considered that, given the small proportion of use of the Q6W regimen and its advice that cemiplimab Q3W was unlikely to replace pembrolizumab Q6W to a significant extent, it was reasonable to base the CMA on the pembrolizumab Q3W dose regimen.

- 7.4 The PBAC considered that the nomination of pembrolizumab monotherapy as the main comparator was appropriate, noting that pembrolizumab is the only immunotherapy that can be used as monotherapy for the proposed PBS population.
- 7.5 The PBAC considered the restriction text in paragraph 3.1 was appropriate with the following amendments:
- Amendment of the clinical criteria: “The condition must express programmed cell death ligand 1 (PD L1) with a tumour score of at least 50% in the tumour sample” to “The condition must express programmed cell death ligand 1 (PD L1) with a tumour proportion score (TPS) of at least 50% in the tumour sample” to more accurately reflect the proposed TGA indication.
 - Addition of the following clinical criteria, as proposed by the Secretariat and agreed to in the PSCR (see paragraph 3.5): “The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition”.
 - The PBAC agreed with the sponsor’s request to delete the following notes from the requested restriction: “A patient may only qualify for PBS subsidised treatment under this restriction once.”; and “Following completion of the initial PBS subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.” The PBAC noted these criteria were specifically associated with grandfathering criteria for pembrolizumab and grandfathering criteria were not requested for cemiplimab.
 - The PBAC advised it was appropriate to clarify the maximum treatment duration for cemiplimab as follows: “The treatment must not exceed a total of 35 cycles or up to 24 months of treatment under both initial and continuing treatment restrictions, whichever comes first”. The PBAC noted that this change is required to flow on to the relevant NSCLC restriction criteria for pembrolizumab.
 - The PBAC advised the population criteria limiting to patients aged 18 years or older could be removed for consistency with other immune checkpoint inhibitors.
- 7.6 The submission was based on an indirect treatment comparison of one randomised cemiplimab trial (Study 1624), which compared cemiplimab monotherapy with platinum-based chemotherapy; and two randomised pembrolizumab trials (KN024 and KN042), which compared pembrolizumab monotherapy with platinum-based chemotherapy. The PBAC noted heterogeneity between the trials affected the transitivity assumptions which may impact interpretation of the indirect comparison

(see paragraphs 6.29 and 6.30). Specifically, the PBAC noted a higher proportion of patients in the cemiplimab trials had squamous histology, were male, and were European, all of which may have favoured cemiplimab.

- 7.7 The PBAC noted the results of the indirect comparison for OS suggested no significant difference in the treatment effect of cemiplimab versus chemotherapy compared with pembrolizumab versus chemotherapy [OS HR: 1.01 (95%CI: 0.74, 1.37)], however the confidence intervals for the indirect comparison were wide. The PBAC noted the indirect comparison of OS using the cemiplimab mITT-1 population (i.e., patients with PD-L1 TPS \geq 50%) also suggested no significant difference, although the point estimate for this comparison favoured cemiplimab [OS HR: 0.84 (95%CI; 0.59, 1.20)].
- 7.8 The PBAC noted the submission's claim that cemiplimab is non-inferior to pembrolizumab in terms of comparative efficacy. The PBAC acknowledged that some uncertainty remained with respect to the indirect comparison between cemiplimab and pembrolizumab due to transitivity issues and wide confidence intervals, but considered that, overall, a conclusion of non-inferior efficacy is supported for cemiplimab compared with pembrolizumab in the proposed indication.
- 7.9 The PBAC noted that wide confidence intervals made an indirect comparison of safety outcomes difficult to interpret (see Table 7). However, the PBAC considered that based on the known safety profiles of PD-L1 inhibitors, the toxicities are likely to be similar, thus supporting a conclusion of non-inferior safety for cemiplimab and pembrolizumab as claimed by the submission.
- 7.10 The PBAC noted uncertainty regarding some of the key assumptions used to determine the projected utilisation of cemiplimab (see paragraph 6.46). However, the PBAC considered that, at a price cost-minimised to the effective price of pembrolizumab, the listing of cemiplimab on the PBS for patients with NSCLC would be expected to result in no additional cost to the PBS/RPBS.
- 7.11 The PBAC advised that cemiplimab would need to join the current RSA applying to atezolizumab, durvalumab, ipilimumab, nivolumab and pembrolizumab for the treatment of NSCLC. The PBAC considered that, because the recommendation to list cemiplimab was on the basis of cost-minimisation and sequential use of the medicines in the RSA is not permitted, no increase in expenditure caps was required.
- 7.12 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because cemiplimab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over pembrolizumab, 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.

- 7.13 The PBAC advised that cemiplimab is not suitable for prescribing by nurse practitioners.
- 7.14 The PBAC recommended that cemiplimab should not be treated as interchangeable with any other drugs.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:

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Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name	Manufacturer
CEMIPLIMAB 350 mg/7 mL injection, 10 mL vial solution for infusion, 1 x 10 mL vial	350 mg	6	Libtayo®	sanofi-aventis Australia Pty Ltd
Category / Program:	Section 100 – Efficient Funding of Chemotherapy Chemotherapy Items for Public Hospital Use Chemotherapy Items for Private Hospital Use			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Severity:	Stage IV (metastatic)			
Condition:	Non-small cell lung cancer (NSCLC)			
PBS Indication:	Stage IV (metastatic) NSCLC			
Treatment phase:	Initial treatment – 3 weekly treatment regimen			
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined			
Clinical criteria:	<ul style="list-style-type: none"> • 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 express programmed cell death ligand 1 (PD-L1) with a tumour proportion score (TPS) of at least 50% in the tumour sample, 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 the sole PBS-subsidised systemic anti-cancer therapy for this condition AND • The treatment must not exceed a total of 7 doses under this restriction. <p><u>Note</u> 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.</p>			

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Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name	Manufacturer
CEMIPLIMAB 350 mg/7 mL injection, 10 mL vial solution for infusion, 1 x 10 mL vial	350 mg	6	Libtayo®	sanofi-aventis Australia Pty Ltd
Category / Program:	Section 100 – Efficient Funding of Chemotherapy Chemotherapy Items for Public Hospital Use Chemotherapy Items for Private Hospital Use			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Severity:	Stage IV (metastatic)			
Condition:	Non-small cell lung cancer (NSCLC)			
PBS Indication:	Stage IV (metastatic) NSCLC			
Treatment phase:	Continuing treatment – 3 weekly treatment regimen			
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined			
Clinical criteria:	<ul style="list-style-type: none"> • Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND • Patient must not have developed disease progression while being treated with this drug for this condition, AND • The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition, AND • The treatment must not exceed a total of 35 cycles or up to 24 months of treatment under both initial and continuing treatment restrictions, whichever comes first. 			

8.2 Flow on changes to pembrolizumab NSCLC criteria:

PBS item codes: 11492W and 11494Y (3 weekly treatment regimen)

Delete from streamlined code 10682: The treatment must not exceed a total of 35 cycles or up to 24 months of treatment under this restriction.

Add: The treatment must not exceed a total of 35 cycles or up to 24 months of treatment under both initial and continuing treatment restrictions, whichever comes first.

PBS item codes: 12119W and 12121Y (6 weekly treatment regimen)

Delete from streamlined code 10693: The treatment must not exceed a total of 18 cycles or up to 24 months of treatment under this restriction.

Add: The treatment must not exceed a total of 18 cycles or up to 24 months of treatment under both initial and continuing treatment restrictions, whichever comes first.

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.