

6.04 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 Section 100 (Efficient Funding of Chemotherapy (EFC)) Authority Required (STREAMLINED) listing for cemiplimab to be used with platinum doublet chemotherapy (PDC) as a first-line treatment of adult patients with Stage IV (metastatic) non-small cell lung cancer (NSCLC) with no evidence of epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or c-ROS proto-oncogene 1 (ROS1) aberrations, irrespective of histology or programmed death ligand (PD-L1) expression levels.⁹⁸ .0
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus pembrolizumab in combination with chemotherapy. 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 with no evidence of an activating EGFR, ALK or ROS1 gene arrangement in tumour material
Intervention	Cemiplimab 350 mg Q3W administered as an IV infusion+PDC
Comparator	Pembrolizumab 200 mg Q3W administered as an IV infusion+PDC
Outcomes	OS, PFS, ORR, quality of life and safety
Clinical claim	For first-line treatment of patients with Stage IV (metastatic) NSCLC, cemiplimab+PDC is non-inferior to pembrolizumab+PDC in terms of comparative effectiveness and safety

Source: Table 1-1, p2 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; PDC = platinum doublet chemotherapy; PFS = progression free survival; Q3W = every 3 weeks; ROS1 = cROS proto oncogene 1.

2 Background

Registration status

- 2.1 Cemiplimab was TGA registered on 5 June 2023 for the following indication: Cemiplimab in combination with platinum-based chemotherapy is indicated for the first-line treatment of patients with NSCLC whose tumours have no EGFR, ALK or ROS1 aberrations and is:
- locally advanced where patients are not candidates for surgical resection or definitive chemoradiation, or
 - metastatic.

- 2.2 Cemiplimab is also TGA approved as monotherapy for the first-line treatment of adult patients with NSCLC expressing PD-L1 tumour proportion score (TPS) $\geq 50\%$ as determined by a validated test, with no EGFR, ALK or ROS1 aberrations, who have locally advanced NSCLC and who are not candidates for surgical resection or 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.

MEDICINAL PRODUCT Form	PBS item codes	Dispensed Price Max Amt	Max. Amount	No. of Rpts
Cemiplimab	13169D (Public) MP 13160P (Private) MP	\$7,378.39 published price (public) \$7,523.58 published price (private)	350 mg	6
Available brands				
Libtayo (Cemiplimab 350 mg/7 mL injection, 7 mL vial)				

Category / Program: Section 100 – Efficient Funding of Chemotherapy - Public and Private Hospitals
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined
Administrative Advice: <i>No increase in the maximum quantity or number of units may be authorised.</i>
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: <i>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.</i>
Severity: Stage IV (metastatic)
Condition: Non-small cell lung cancer (NSCLC)
Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment Phase: Initial treatment – 3 weekly treatment regimen
Clinical criteria: Patient must not have previously been treated for this condition in the metastatic setting; OR The condition must have progressed after treatment with tepotinib,
AND
Clinical criteria: Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for non-small cell lung cancer,
AND
Clinical criteria: Patient must have a WHO performance status of 0 or 1,
AND

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Clinical criteria:
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
Clinical criteria:
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
Clinical criteria:
The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition
AND
Clinical criteria:
The treatment must not exceed a total of 7 doses under this restriction.

MEDICINAL PRODUCT Form	PBS item codes	Dispensed Price Max Amt	Max. Amount	No. of Rpts
Cemiplimab	13161Q (Public) MP	\$7,378.39 published price (public)	350 mg	6
	13162R (Private) MP	\$7,523.58 published price (private)		
Available brands				
Libtayo (Cemiplimab 350 mg/7 mL injection, 7 mL vial)				

Category / Program: Section 100 – Efficient Funding of Chemotherapy - Public and Private Hospitals
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
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.
Severity: Stage IV (metastatic)
Condition: Non-small cell lung cancer (NSCLC)
Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment Phase: Continuing treatment – 3 weekly treatment regimen
Clinical criteria:
Patient must have previously received PBS subsidised treatment with this drug for this condition,
AND
Clinical criteria:
Patient must not have developed disease progression while being treated with this drug for this condition,
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition

AND
Clinical criteria:
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.

- 3.2 The submission stated that the sponsor would seek a Special Pricing Arrangement (SPA).
- 3.3 The submission requested a combined listing for cemiplimab 350 mg to allow its use as a monotherapy or in combination with PDC in Stage IV NSCLC. Overall, the wording of the proposed PBS restriction for cemiplimab was similar to the listing of pembrolizumab for the treatment of Stage IV NSCLC. The Economic Sub-Committee (ESC) considered this was appropriate.
- 3.4 The sponsor requested listing that matches the current 3-weekly treatment regimen NSCLC listing of the main comparator pembrolizumab. Previously, pembrolizumab was listed on the PBS, as monotherapy, for treatment of NSCLC patients with high expression of PD-L1 (i.e., TPS \geq 50%). Following the positive Pharmaceutical Benefits Advisory Committee (PBAC) recommendation for pembrolizumab in combination with chemotherapy, for treatment of NSCLC, regardless of PD-L1 expression, the pembrolizumab listing was consolidated to allow clinicians to determine to use pembrolizumab in combination with chemotherapy or as monotherapy 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). As a result, the current PBS restrictions for pembrolizumab (11492W private, 11494Y public) do not differentiate between use of pembrolizumab as monotherapy or in combination with PDC, nor include a criterion on PD-L1 expression level. Cemiplimab monotherapy is currently PBS listed for Stage IV NSCLC in patients expressing PD L1 with a TPS \geq 50%.
- 3.5 The proposed PBS population limits the use of cemiplimab to patients with Stage IV NSCLC. This was different from the key clinical trial (Study 16113) and the TGA indication, which included patients with both Stage III (locally advanced) and Stage IV patients with NSCLC.
- 3.6 The requested listing included administrative advice noting a SPA applies and that no increases to the maximum number of repeats may be authorised. The Secretariat added an advice to also state that no increases to the maximum amount or number of units may be authorised, as cemiplimab does not have a variable dose regimen.
- 3.7 The submission stated that there is currently not adequate evidence to support retreatment with PD-L1 inhibitors. The PBAC considered treatment with a PD-L1 inhibitor for NSCLC should continue to be limited to one course per lifetime until such time that clinical evidence is provided to support retreatment.
- 3.8 The submission did not propose a grandfather restriction.

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 cancer death and the fifth most diagnosed cancer in Australia¹. NSCLC accounts for 85-90% of lung cancer cases², and approximately 40% of NSCLC patients present with Stage IV (metastatic) disease at the time of diagnosis³. Compared to other stages, the prognosis for patients with Stage IV disease is generally poor, with a 5-year relative survival rate of 3.2% in 2011-2016⁴.
- 4.2 The submission proposed cemiplimab in combination with PDC (hereafter referred to as cemiplimab+PDC) to be used as first-line treatment in patients with Stage IV NSCLC without EGFR, ALK and ROS1 aberrations, regardless of histology and PD-L1 expression levels.
- 4.3 Clinical practice guidelines, such as European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN), recommend the following treatments for Stage IV NSCLC without contraindications for immunotherapy and based on tumour proportion score (TPS) and performance status (PS).

Table 2: Groups of metastatic NSCLC without contraindications for immunotherapy and their preferred treatments

No.	Metastatic NSCLC without contraindication for ICI	Preferred treatment
1	PS 0-2 and PD-L1 TPS \geq 50%	ICI monotherapy
2	PS 0-1, irrespective of PD-L1 TPS	Combination therapy, ICI with PDC
3	PS 2, PD-L1 TPS <50%	PDC or single agent chemotherapy
4	PS 3-4, irrespective of PD-L1 TPS	Best supportive care

Source: ESMO clinical practice guidelines for non-oncogene addicted metastatic non-small cell lung cancer

ICI = Immune-check point inhibitor; NSCLC = non-small cell lung cancer; PDC = platinum-doublet chemotherapy; PD-L1 = programmed cell death ligand 1; PS = performance status; TPS = tumor propensity score.

- 4.4 The ESC noted the clinical treatment algorithm in the current submission generally aligns with contemporary practice recommendations (ESMO 2023; NCCN 2023). Approximately 25-35% of Stage IV NSCLC patients without EGFR, ALK and ROS1 aberrations have a PD-L1 TPS \geq 50%. Given that cemiplimab, as a monotherapy, is PBS listed for the treatment of patients with Stage IV NSCLC without EGFR, ALK and ROS1 aberrations and PD-L1 TPS \geq 50%, these patients could either be treated with cemiplimab monotherapy or cemiplimab+PDC combination, based on clinical discretion.
- 4.5 Cemiplimab is a fully recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that targets the PD-1 receptor and is part of the pharmacological class of PD-

¹ Cancer Australia, (2022), Lung cancer in Australia statistics. Available at: <https://www.canceraustralia.gov.au/cancer-types/lung-cancer/statistics>.

² Cancer Australia, (2022), Types of lung cancer. Available at: <https://www.canceraustralia.gov.au/cancer-types/lung-cancer/types>.

³ National Cancer Control Indicators. Available at [National cancer stage at diagnosis data | National Cancer Control Indicators \(canceraustralia.gov.au\)](https://www.canceraustralia.gov.au/national-cancer-control-indicators)

⁴ Australian Institute of Health and Welfare, (2022), 'Cancer data in Australia. Cancer incidence and survival by stage data visualisation'. Available at: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-incidence-and-survival-by-stage-data-visualisation>

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.

5 Comparator

5.1 The submission nominated pembrolizumab in combination with chemotherapy (hereinafter referred to as pembrolizumab+PDC) as the main comparator. The main argument provided in support of this nomination was:

- Pembrolizumab is the only PBS listed treatment that can be used in combination with PDC in patients with Stage IV NSCLC without EGFR, ALK or ROS1 aberrations, irrespective of histology or PD-L1 expression. The ESC considered that the submission's nomination of pembrolizumab+PDC as the main comparator was appropriate.

5.2 However, two other combination treatments based on histology are currently listed on the PBS for Stage IV NSCLC without evidence of genetic aberrations and may be relevant alternative therapies. These include: atezolizumab+bevacizumab+PDC for non-squamous NSCLC and nivolumab+ipilimumab+PDC for squamous NSCLC. Some patients within the proposed population (i.e., PD-L1 TPS $\geq 50\%$) may be treated with pembrolizumab or cemiplimab monotherapy.

5.3 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under *Section 101(3B) of the National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

5.4 For the requested population, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: pembrolizumab+PDC, atezolizumab+bevacizumab+PDC, nivolumab+ipilimumab+PDC, pembrolizumab monotherapy and cemiplimab monotherapy.

5.5 The PBAC noted pembrolizumab+PDC and cemiplimab+PDC were intended for similar patient populations in terms of histology and PD-L1 expression, with the other treatments referred to in paragraph 5.4 limited to subgroups of patients.

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 Lung Foundation Australia via the Consumer Comments facility on the PBS website. Lung Foundation Australia described the potential benefits of the listing of cemiplimab on the PBS including providing patients with an additional treatment choice.

Clinical trials

- 6.3 In the absence of head-to-head trials, the submission presented an indirect treatment comparison (ITC), using the Bucher method, comparing one cemiplimab+PDC trial with a meta-analysis of two pembrolizumab+PDC trials, with placebo+PDC as the common reference. The submission was based on the following randomised trials.
- Part 2 of Study 16113 (N=466) is an ongoing Phase III, multicentre, randomised, double-blinded, placebo-controlled trial of cemiplimab+PDC in adult patients with Stage III or Stage IV NSCLC without EGFR, ALK and ROS1 genomic mutations and who had not previously received systemic therapy for advanced NSCLC. Patients were randomised (2:1) based on histology (non-squamous and squamous) and PD-L1 expression (<1%, 1% to 49%, ≥50%).
 - KN-189 (N=616) is a completed Phase III, multicentre, randomised, double-blind, placebo-controlled trial of pembrolizumab+PDC in adult patients with Stage IV NSCLC with non-squamous histology without EGFR and ALK genomic mutations and who had not previously received systemic therapy for advanced NSCLC. Patients were randomised (2:1) based on PD-L1 expression (<1% vs. ≥1%), PDC regimen (cisplatin vs. carboplatin), smoking status (never smoker vs. former/current smoker).
 - KN-407 (N=559) is an ongoing Phase III, multicentre, randomised, double-blind, placebo-controlled trial of pembrolizumab+PDC in adult patients with Stage IV NSCLC with squamous histology and who had not previously received systemic therapy for advanced NSCLC. Patients were randomised (1:1) based on PD-L1 expression (<1% vs. ≥1%), PDC regimen (paclitaxel vs. nab-paclitaxel), and geographic region (East Asia vs. rest of the world).
- 6.4 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Cemiplimab+PDC trials		
Study 16113 (NCT03409614)	<p>A two part randomised, Phase 3 study of combinations of cemiplimab (anti-PD-1 antibody) and platinum based doublet chemotherapy in first line treatment of patients with advanced or metastatic non-small cell lung cancer.</p> <p>Gogishvili M., et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomised, controlled, double-blind phase 3 trial.</p> <p>Makharadze T., et al. Cemiplimab Plus Chemotherapy Versus Chemotherapy Alone in Advanced NSCLC: 2-Year Follow-Up From the Phase 3 EMPOWER-Lung 3 Part 2 Trial.</p> <p>Makharadze T., et al. Quality of life with cemiplimab plus chemotherapy for first-line treatment of advanced non-small cell lung cancer: Patient-reported outcomes from phase 3 EMPOWER-Lung 3.</p>	<p>June 2022</p> <p><i>Nature Medicine</i> 2022; 28(11):2374-2380.</p> <p><i>Journal of Thoracic Oncology</i> 2023; 18(6):755-768</p> <p><i>Cancer</i> 2023; 129(14): 2256-2265.</p>
Pembrolizumab+PDC trials		
KN-189 (NCT02578680)	<p>Study of pemetrexed+platinum chemotherapy with or without pembrolizumab (MK-3475) in participants with first line metastatic non squamous non-small cell lung cancer (MK-3475-189/KEYNOTE 189).</p> <p>Gandhi L., et al. Pembrolizumab plus chemotherapy in metastatic non-small cell lung cancer.</p> <p>Gadgeel S., et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic non squamous non-small cell lung cancer.</p> <p>Garassino MC., et al. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, Phase 3 trial.</p> <p>Rodriguez-Abreu, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic non-squamous NSCLC: protocol-specified final analysis from KEYNOTE-189.</p> <p>Garassino MC., et al. Pembrolizumab plus pemetrexed and platinum in non-squamous non-small cell lung cancer: 5-year outcomes from the Phase 3 KEYNOTE-189 study.</p>	<p>March 2022</p> <p><i>New England Journal of Medicine</i> 2018; 378(22): 2078-2092.</p> <p><i>Journal of Clinical Oncology</i> 2020; 38(14):1505-1517.</p> <p><i>Lancet Oncology</i> 2020; 21(3):387-397.</p> <p><i>Annals of Oncology</i> 2021; 32(7):881-895.</p> <p><i>Journal of Clinical Oncology</i> 2023; 41(11):1992-1998.</p>
KN-407 (NCT02775435)	<p>A study of carboplatin paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in adults with first line metastatic squamous non-small cell lung cancer (MK-3475-407/KEYNOTE 407)</p> <p>Paz Ares L., et al. Pembrolizumab plus chemotherapy for squamous non-small cell lung cancer.</p> <p>Mazieres J., et al. 2019. Health Related quality of life with carboplatin paclitaxel or nab paclitaxel with or without pembrolizumab in patients with metastatic squamous non-small cell lung cancer.</p> <p>Paz Ares L., et al. 2020. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol specified final analysis of KEYNOTE 407.</p> <p>Novello S., et al. 2023. Pembrolizumab plus chemotherapy in squamous non-small cell lung cancer: 5-year update of the Phase III KEYNOTE 407 study.</p>	<p>February 2022</p> <p><i>New England Journal of Medicine</i> 2018; 379(21):2040-2051.</p> <p><i>Journal of Clinical Oncology</i> 2020; 38(3):271-280.</p> <p><i>Journal of Thoracic Oncology</i> 2020; 15(10):1657-1669.</p> <p><i>Journal of Clinical Oncology</i> 2023; 41(11):1999-2006.</p>

Source: Table 2-6, p20 and Table 2-7, pp20-22 of the submission.

6.5 The key features of evidence included in the ITC are summarised in Table 4.

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

Trial	N	Design/ Median follow-up	Risk of bias	Patient population	Outcome(s)
Cemiplimab+PDC vs. PDC					
Study 16113	466	R, DB, MC, 28.4 months (June 2022 data cutoff)	Low	Squamous and non-squamous NSCLC patients with Stage III or IV (metastatic) disease.	OS, PFS, ORR, AEs, QoL
Pembrolizumab+PDC vs PDC					
KN-189	616	R, DB, MC, 64.6 months (March 2022 data cutoff)	Low	Non-squamous NSCLC patients with Stage IV (metastatic) disease.	OS, PFS, ORR, AEs, QoL
KN-407	559	R, DB, MC, 56.9 months (February 2022 data cutoff)	Low	Squamous NSCLC patients with Stage IV (metastatic) disease.	OS, PFS, ORR, AEs, QoL
Meta-analysis	Included KN-189 and KN-407; assessed OS, PFS, ORR and AEs				

Source: Table ES.5, p8 and Section 2.6.3, pp70-79 of the submission.

AE = adverse event; DB = double blind; MC = multi-centre; N = total number of participants; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression-free survival; QoL = quality of life; R = randomised.

- 6.6 In Study 16113, OS was the primary efficacy outcome, with progression-free survival (PFS), objective response rate (ORR), quality of life (QoL), and safety as secondary outcomes. In KN-189 trial, PFS was the primary endpoint, with ORR, OS, duration of response (DOR), and safety as secondary endpoints. Exploratory endpoints included the effect of PD-L1 expression on efficacy and patient-reported outcomes (PROs). In KN-407 trial, OS and PFS were the primary endpoints, with ORR, DOR and safety as secondary endpoints and the effect of PD-L1 expression on efficacy and PROs exploratory endpoints. The safety population included all randomised patients who received at least one dose of any study drug.
- 6.7 For cemiplimab+PDC, the results were based on the updated analysis of Study 16113 (data cut-off: June 2022). The results for pembrolizumab+PDC were based on the five-year follow-up data from KN-189 (data cut-off: March 2022) and KN-407 (data cut-off: February 2022). The results from the five-year follow-up for pembrolizumab+PDC may not be comparable to those of cemiplimab+PDC due to a significant difference in the median duration of follow-up in Study 16113 (28.4 months) compared to KN-189 (64.6 months) and KN-407 (56.9 months).
- 6.8 The key differences in the baseline characteristics and treatments across the cemiplimab trial (Study 16113) and the two pembrolizumab trials (KN-189 and KN-407) that may affect the transitivity assumptions are summarised below:
- Study 16113 enrolled patients with Stage III NSCLC (14.8%) and Stage IV NSCLC (85.2%), whereas KN-189 and KN-407 only enrolled patients with Stage IV NSCLC. However, this difference is unlikely to significantly affect the applicability of the trial results to the target population, given the relatively small proportion of patients with Stage III disease in Study 16113 (14.8%).

- Study 16113 enrolled patients with both squamous (57.4%) and non-squamous (43%) NSCLC; most patients enrolled in KN-189 had non-squamous (96.1%) and KN-407 had squamous (97.7%) NSCLC. Subgroup analyses from Study 16113 showed no impact of histology on OS (HR of 0.61 [95% CI: 0.42, 0.87] vs. 0.64 [95% CI: 0.47, 0.88]) and PFS (HR of 0.56 [95% CI: 0.41, 0.78] vs. 0.53 [95% CI: 0.39, 0.71]).
- KN-189 (48.0%) and KN-407 (45.7%) had a higher proportion of patients aged <65 years compared to Study 16113 (41.0%). The subgroup analyses from Study 16113 showed relatively higher benefit in patients aged <65 years when compared to >65 years; this may favour pembrolizumab+PDC.
- Study 16113 (85.2%) and KN-407 (81.4%) had more male patients than KN-189 (58.9%). Subgroup analyses from KN-189 and KN-407 trials showed that there was a lower relative benefit of pembrolizumab+PDC compared to placebo+PDC for males, whereas there was a higher relative benefit of cemiplimab+PDC for males in Study 16113; this may favour cemiplimab+PDC.
- Study 16113 had a higher proportion of patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 (84.3%) compared with KN-189 (56.2%) and KN-407 (70.8%). This difference in ECOG PS among trials may favour pembrolizumab+PDC.
- KN-189 had a higher proportion of patients with brain metastases (17.5%) compared with Study 16113 (6.7%) and KN-407 (7.8%). The prognosis for patients with brain metastasis is relatively poor and may favour cemiplimab+PDC.
- KN-407 had a higher proportion of current/former smokers (92.7%) compared with Study 16113 (85.6%) and KN-189 (88.1%). The subgroup analyses from Study 16113 showed that non-smokers had relatively lower OS (HR of 0.85; 95% CI: 0.45, 1.62 vs. 0.58; 95% CI: 0.45, 0.75) and PFS (HR of 0.66; 95% CI: 0.37, 1.17 vs. 0.52; 95% CI: 0.41, 0.66) benefits compared to smokers. This may favour cemiplimab+PDC.
- Study 16113 had a higher proportion of patients from Europe (87.6%), primarily from Eastern Europe, compared with KN-189 (60.7%) and KN-407 (19.0%). Of note, smoking is more common in Eastern Europe than in the United States, especially among men⁵. As stated above, smokers and men had relatively higher OS and PFS benefits in Study 16113; this may favour cemiplimab+PDC.
- Study 16113 had a higher proportion of patients with PD-L1≥1% (70.2%) compared with KN-189 (62.9%) and KN-407 (63.1%). The subgroup analyses from Study 16113 showed that patients with PD-L1≥1% had improved OS (HR of 0.50; 95% CI:

⁵ Sung, H, et al., (2021), 'Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.' CA: A Cancer Journal for Clinicians, 71, 209–249.

0.34, 0.74 vs 0.94; 95% CI: 0.62, 1.42) and PFS (HR of 0.48; 95% CI: 0.32, 0.72 vs 0.73; 95% CI: 0.50, 1.08) compared to patients with PD-L1<1%; this may favour cemiplimab+PDC.

- 6.9 The ESC noted that in both the KN-189 and KN-407 trials, cross-over to pembrolizumab monotherapy was permitted upon disease progression, whereas no crossover was allowed in Study 16113 protocol. At the most recent data cut-off, the percentage of patients who received pembrolizumab or PD-1/PD-L1 directed therapy in the placebo+PDC arm was 57.3% for KN-189 and 50.9% for KN-407. In Study 16113 (data cut-off: June 2022) approximately 14.9% in the placebo+PDC arm received immunotherapy after disease progression.
- 6.10 The evaluation considered there was potential for bias in both directions. For example, gender, smoking status and geographic region could have biased the ITC results in favour of cemiplimab, whereas age and performance status could have biased the ITC results against cemiplimab. Furthermore, the evaluation considered that the effect of crossover after disease progression in both treatment arms could not be reliably determined, given the difference in treatments received by patients after progression.

Comparative effectiveness

- 6.11 The OS and PFS results for the ITT population in Study 16113 are presented in Table 5.

Table 5: Summary of survival outcomes in Study 16113

	Cemiplimab+PDC n/N (%)	Placebo+PDC n/N (%)	Absolute difference	HR (95% CI)
Overall survival				
Patients with event	180/312 (57.7%)	111/154 (72.1%)	-	-
Median OS months (95% CI)	21.1 (15.9, 23.5)	12.9 (10.6, 15.7)	8.2 months	0.65 (0.51, 0.82)
Progression-free survival				
Patients with event	234/312 (75.0%)	133/154 (86.4%)	-	-
Median PFS months (95% CI)	8.2 (6.4, 9.0)	5.5 (4.3, 6.2)	2.7 months	0.55 (0.44, 0.68)

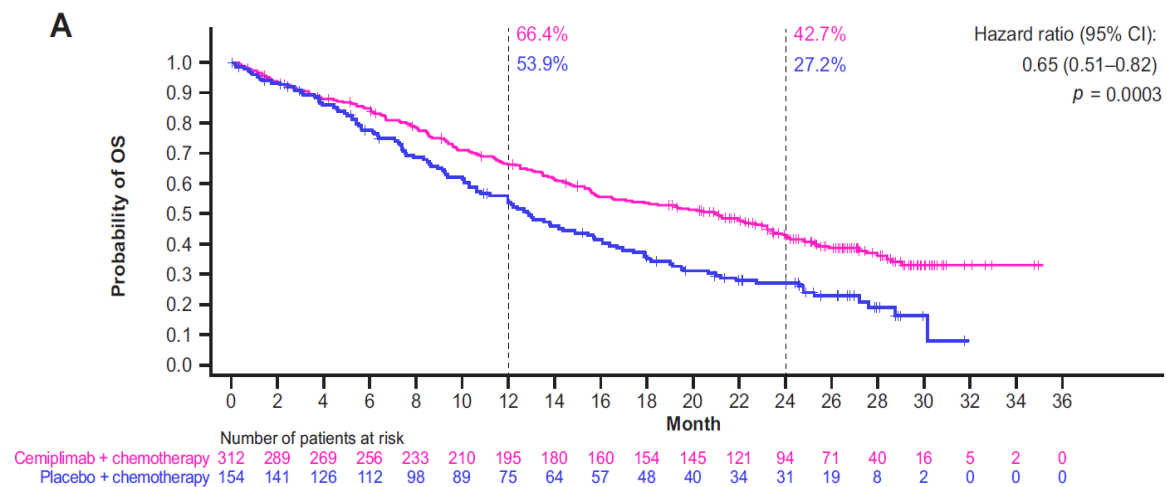
Source: Table 2-22, p53 and Table 2-23, p54 of the submission.

CI = confidence interval; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; OS = overall survival; PDC = platinum-doublet chemotherapy; PFS = progression-free survival.

Bold indicates statistical significance.

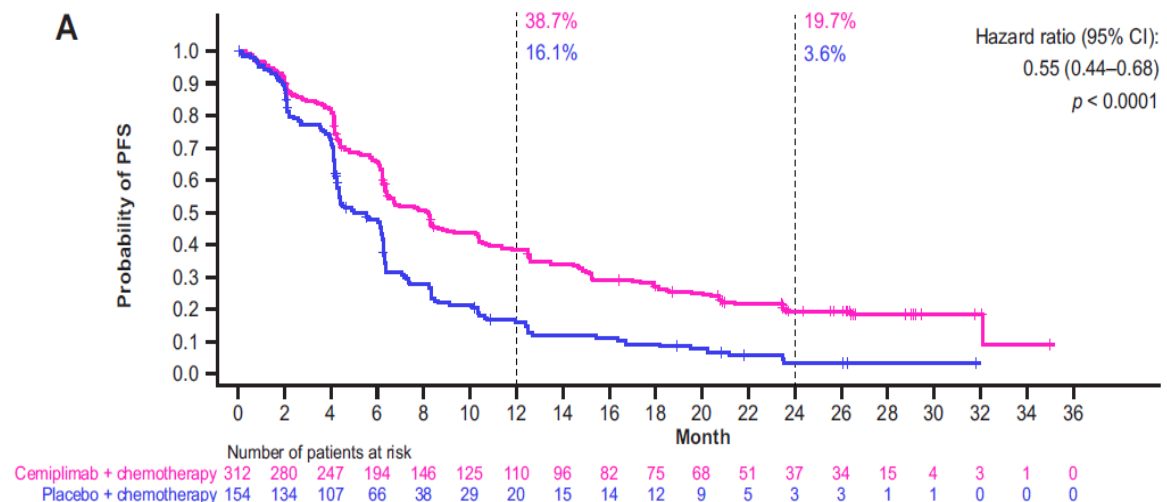
- 6.12 The median OS in the cemiplimab+PDC arm was 8.2 months longer than that in the placebo+PDC arm (21.1 months versus 12.9 months); and the difference was statistically significant (HR: 0.65; 95% CI: 0.51, 0.82). Furthermore, the median PFS in the cemiplimab+PDC arm was 2.7 months longer than that in the placebo+PDC arm (8.2 months versus 5.5 months); and the difference was statistically significant (HR: 0.55; 95% CI: 0.44, 0.68).
- 6.13 Figure 1 and Figure 2 present the Kaplan-Meier plots of OS and PFS for Study 16113.

Figure 1: KM curves of OS in Study 16113



Source: Figure 2-8, p53 of the submission.
 CI = confidence interval, KM = Kaplan-Meier, OS = overall survival.

Figure 2: KM curve of PFS in in Study 16113



Source: Figure 2-9, p54 of the submission.
 CI = confidence interval, KM = Kaplan-Meier, PFS = progression-free survival.

6.14 The ORR, a secondary outcome, was significantly greater in the cemiplimab+PDC arm (43.6%; 95% CI: 38.0, 49.3) compared with placebo+PDC arm (22.1%; 95% CI: 15.8, 29.5). Quality-of-life was measured using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC-QLQ-C30 and EORTC-QLQ-LC13). There was no overall significant difference in functioning scales and symptoms scores between the treatment arms (0.61; 95% CI: 2.23, 3.45); however, there was a statistically significant overall difference in pain symptoms between treatment arms, favouring cemiplimab+PDC arm (4.98; 95% CI: 8.36, 1.60).

KN-189 and KN-407

6.15 The OS and PFS results for the ITT population in KN-189 and KN-407 trials are presented in Table 6.

Table 6: Summary of survival outcomes in KN-189 and KN-407 trials

KN-189	Pembrolizumab+PDC n/N (%)	Placebo+PDC n/N (%)	Absolute difference	HR (95% CI)
Overall survival				
Patients with event	329/410 (80.2%)	183/206 (88.8%)	-	-
Median OS months (95% CI)	22.0 (19.5, 24.5)	10.6 (8.7, 13.6)	11.4 months	0.60 (0.50, 0.72)
Progression-free survival				
Patients with event	369/410 (90.0%)	201/206 (97.6%)	-	-
Median PFS months (95% CI)	9.0 (8.1, 10.4)	4.9 (4.7, 5.5)	4.1 months	0.50 (0.42, 0.60)
KN-407	Pembrolizumab+PDC n/N (%)	Placebo+PDC n/N (%)	Absolute difference	HR (95% CI)
Overall survival				
Patients with event	225/278 (80.9%)	248/281 (88.3%)	-	-
Median OS months (95% CI)	17.2 (14.4, 19.7)	11.6 (10.1,13.7)	5.6 months	0.71 (0.59, 0.85)
Progression-free survival				
Patients with event	241/278 (86.7%)	265/281 (94.3%)	-	-
Median PFS months (95% CI)	8.0 (6.3, 8.5)	5.1 (4.3, 6.0)	2.9 months	0.62 (0.52, 0.74)

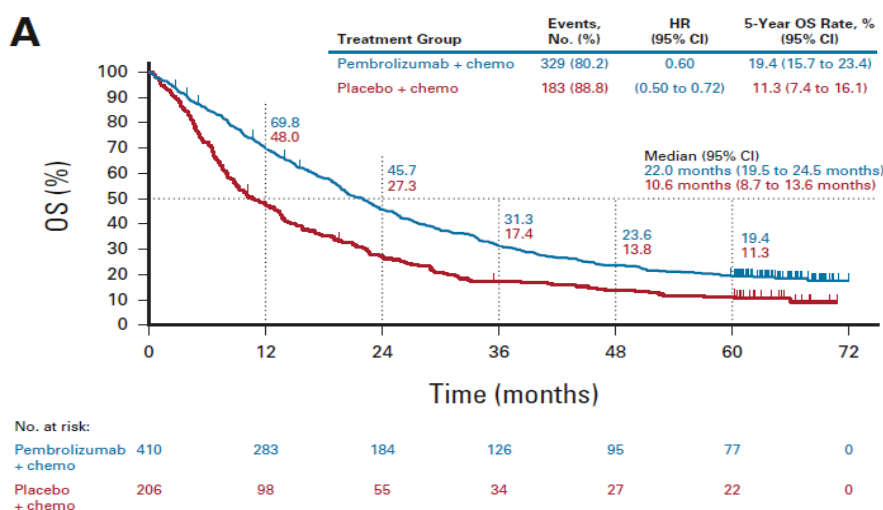
Source: Figure 2-10, p55; Figure 2-11, p56; Figure 2-12, p57 and Figure 2-13, p58 of the submission.

CI = confidence interval; HR = hazard ratio; OS = overall survival; n = number of participants reporting data; N = total participants in group; PDC = platinum-doublet chemotherapy; PFS = progression-free survival.

6.16 In KN-189, pembrolizumab+PDC was associated with statistically significant improvement in OS (HR: 0.60; 95% CI: 0.50, 0.72) and PFS (HR: 0.50; 95% CI: 0.42, 0.60) compared to placebo+PDC. Similarly, pembrolizumab+PDC was associated with statistically significant improvement in OS (HR: 0.71; 95% CI: 0.59, 0.85) and PFS (HR: 0.62; 95% CI: 0.52, 0.74) compared to placebo+PDC in KN-407.

6.17 Figure 3 and Figure 4 presents the Kaplan-Meier plot of OS and PFS for KN-189.

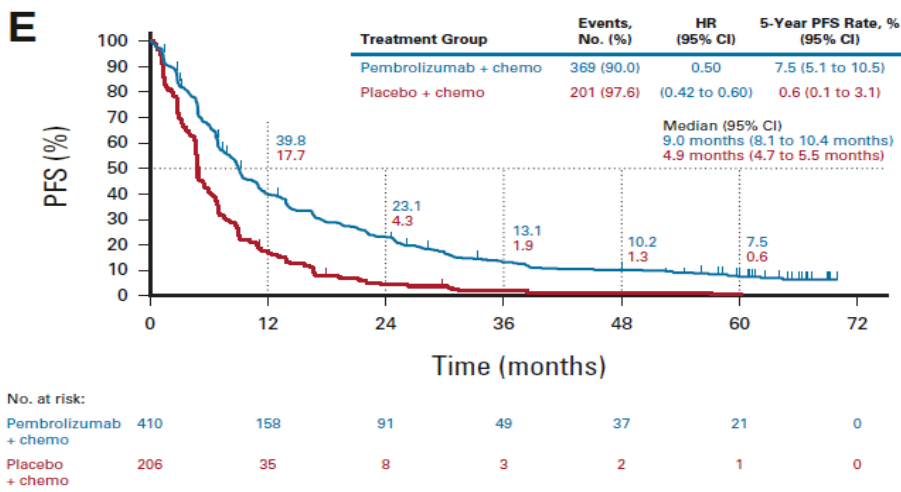
Figure 3: KM curve of OS in KN-189



Source: Figure 2-10, p55 of the submission.

CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier, OS = overall survival.

Figure 4: KM curve of PFS in KN-189

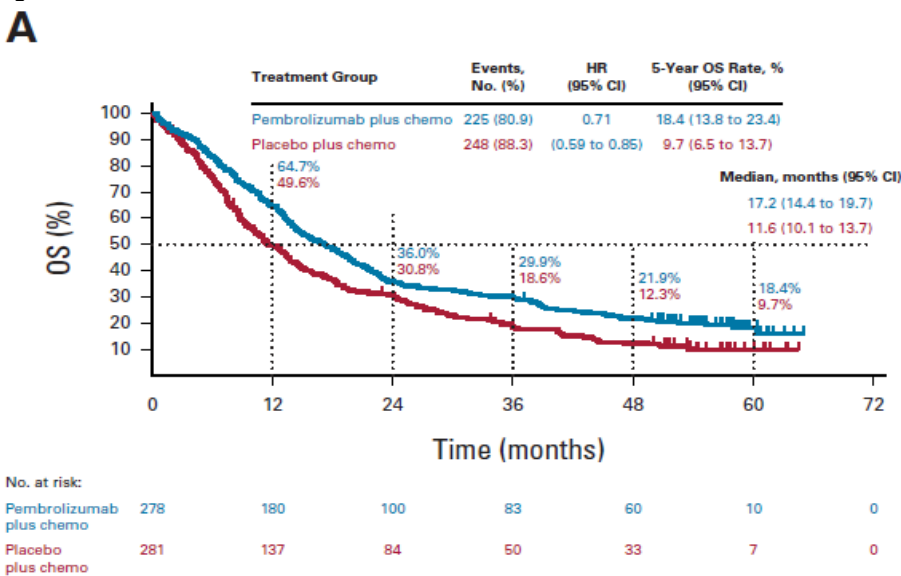


Source: Figure 2-11, p56 of the submission.

CI = confidence interval, HR = hazard ratio; KM = Kaplan-Meier, PFS = progression-free survival.

6.18 Figure 5 and Figure 6 presents the Kaplan-Meier plot of OS and PFS for KN-407.

Figure 5: KM curve of OS in KN-407

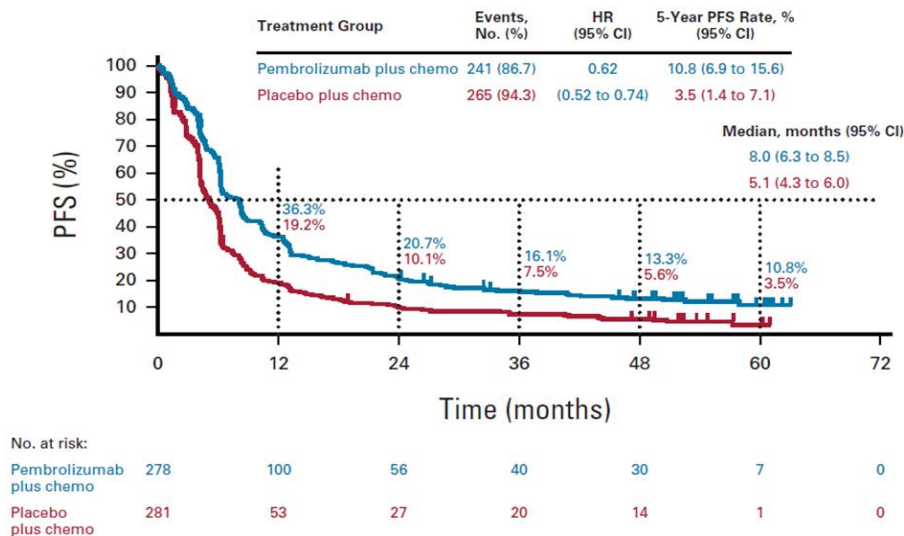


Source: Figure 2-12, p57 of the submission.

CI = confidence interval, HR = hazard ratio; KM = Kaplan-Meier, OS = overall survival.

Figure 6: KM curve of PFS in KN-407

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Source: Figure 2-13, p58 of the submission.

CI = confidence interval, HR = hazard ratio; KM = Kaplan-Meier, PFS = progression-free survival.

Subgroup analyses

- 6.19 The submission also presented pre-specified subgroup analyses of primary outcomes to inform the exchangeability of cemiplimab+PDC and pembrolizumab+PDC trials.
- 6.20 In Study 16113, compared to the placebo+PDC arm, cemiplimab+PDC demonstrated improved survival in most sub-groups, except for the following subgroups where the 95% CI crosses the point estimate of 1: patients aged ≥ 65 years, females, ethnicities other than white, PD-L1 expression $< 1\%$ and non-smokers. Furthermore, patients in the cemiplimab+PDC had improved PFS in most sub-groups except for the following subgroups where the 95% CI crosses the point estimate of 1: females, ethnicities other than white, PD-L1 expression $< 1\%$ and brain metastasis. The submission stated that due to limited events and a small number of patients, the confidence interval of the hazard ratio crossed 1. Moreover, certain subgroups, such as females and non-smokers, may have a common confounding factor.
- 6.21 Subgroup analyses from Study 16113 highlighted that patients with PD-L1 expression $\geq 1\%$ drove the main benefits in terms of both OS and PFS. For the PD-L1 $< 1\%$ subgroup, which constituted around a third of the ITT population (139 patients, 30%), lower median OS was reported in the cemiplimab+PDC arm (12.8 months) compared to the placebo+PDC (14.2 months) arm in the primary analysis, with a HR of 1.006 (95% CI: 0.63, 1.60). In the updated analyses the HR for OS of was 0.94 (95% CI: 0.62, 1.42) within this subgroup.
- 6.22 Subgroup analysis from KN-189 and KN-407 suggested a trend for higher survival benefit with pembrolizumab+PDC compared to placebo+PDC in patients with PD-L1 $< 1\%$, with an OS HR of 0.51 (95% CI: 0.36, 0.71) and 0.61 (95% CI: 0.38, 0.98), respectively.

Meta-analysis of pembrolizumab trials (KN-189 and KN-407)

- 6.23 The submission conducted a meta-analysis of KN-189 and KN-407 to obtain pooled results of pembrolizumab+PDC for indirect comparison with cemiplimab+PDC. This was appropriate to facilitate indirect comparison as KN-189 enrolled non-squamous NSCLC patients, KN-407 enrolled squamous NSCLC patients, while Study 16113 included both squamous and non-squamous NSCLC patients.
- 6.24 The submission stated that the degree of heterogeneity in terms of OS and PFS between KN-189 and KN-407 was not statistically significant.
- 6.25 For ORR, the heterogeneity between the two trials varied, depending on the measure of effect (odds ratio (OR), relative risk (RR) or risk difference (RD)). OR showed moderate heterogeneity and RD showed minimal heterogeneity; however, these were not statistically significant. In contrast, RR showed statistically significant heterogeneity.
- 6.26 There was minimal heterogeneity in most of the safety outcomes and the observed differences in these outcomes in the individual trials (KN-189 and KN-407) could be attributed to sample size variations. Of note, there were high levels of heterogeneity in the RD for AEs leading to discontinuation ($I^2=75%$) and a moderate level of heterogeneity in the RD of AEs leading to death ($I^2=38%$).

Indirect Treatment Comparison

- 6.27 The submission presented an ITC, using the Bucher method, comparing Study 16113 with a meta-analysis of estimates from KN-189 and KN-407, using placebo+PDC as the common reference. The ITC results of OS and PFS are summarised in Table 7.

Table 7: Summary of results of the indirect comparison for OS and PFS

Trial type or estimate	Trial ID	N	PD-1 inhibitor+PDC	N	Placebo+PDC	HR
OS						
Cemiplimab+PDC vs. placebo+PDC	16113	312	21.1 (15.9, 23.5)	154	12.9 (10.6, 15.7)	0.65 (0.51, 0.82)
Pembrolizumab+PDC vs. placebo+PDC	KN-189	410	22.0 (19.5, 24.5)	206	10.6 (8.7, 13.6)	0.60 (0.50, 0.72)
	KN-407	278	17.2 (14.4, 19.7)	281	11.6 (10.1, 13.7)	0.71 (0.59, 0.85)
	KN meta-analysis k=2					0.65 (0.55, 0.77)
ITC cemiplimab+PDC vs. pembrolizumab+PDC	16113 vs. KN meta-analysis					1.00 (0.75, 1.34)
PFS						
Cemiplimab+PDC vs. placebo+PDC	16113	312	8.2 (6.4, 9.0)	154	5.5 (4.3, 6.2)	0.55 (0.44, 0.68)
Pembrolizumab+PDC vs. placebo+PDC	KN-189	410	9.0 (8.1, 10.4)	206	4.9 (4.7, 5.5)	0.50 (0.42, 0.60)
	KN-407	278	8.0 (6.3, 8.5)	281	5.1 (4.3, 6.0)	0.62 (0.52, 0.74)
	KN meta-analysis k=2					0.56 (0.45, 0.69)
ITC cemiplimab+PDC vs. pembrolizumab+PDC	16113 vs. KN meta-analysis					0.98 (0.72, 1.33)

Source: Table 2-32, p79 and Table 2-33, p80 of the submission.

CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; ITT = intention-to treat; k = number of studies contributing to the pooled estimates of effect; N = total participants in group; OS = overall survival; PDC = platinum doublet chemotherapy; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival.

Bold indicates statistical significance.

- 6.28 The ESC noted the indirect comparison of efficacy showed no significant difference in OS between cemiplimab+PDC and pembrolizumab+PDC (HR: 1.00; 95% CI: 0.75, 1.34). The 95% CI contained an increase in hazard for death by 34%, which could be clinically important to the proposed target population.
- 6.29 Similarly, there was no significant difference in PFS between cemiplimab+PDC and pembrolizumab+PDC (HR: 0.98; 95% CI: 0.72, 1.33).
- 6.30 The indirect comparison showed no significant difference in ORR between cemiplimab+PDC and pembrolizumab+PDC (RR: 1.02; 95% CI: 0.60, 1.72).
- 6.31 Results from the ITC suggest that cemiplimab+PDC is non-inferior to pembrolizumab+PDC; however, these results are difficult to interpret due to heterogeneities across the trials, in terms of stratification factors, histology, disease stage, gender, ECOG performance status, presence of brain metastases at diagnosis, which affect the transitivity assumption that forms the basis of ITC between cemiplimab+PDC and pembrolizumab+PDC. The pre-PBAC Response acknowledged that the results of the ITC were subject to uncertainty due to the inherent nature of the comparison and stated that there was potential for bias in either direction. The pre-PBAC Response highlighted that the median OS and PFS in the placebo+PDC arms of the cemiplimab trial and the pembrolizumab trials were similar, with overlapping

95% CIs (median OS of 12.9, 10.6, 11.6, and median PFS of 5.5, 4.9, 5.1 in study 16113, KN-189, KN-407 respectively), supporting the robustness and validity of the ITC. The ESC considered the ITC had a high risk of bias.

- 6.32 The ESC noted the submission did not present a matching-adjusted indirect comparison (MAIC) to adjust for the heterogeneities in the baseline characteristics and demographics. Of note, Halmos et al. (2020) conducted an anchored MAIC to estimate the efficacy of pembrolizumab+PDC against nivolumab+ipilimumab patients and identified age group, gender, region, smoking status, ECOG-PS, brain metastasis, PD-L1 expression, disease at baseline and histology to be potential effect modifiers. The pre-PBAC Response maintained that the network meta-analysis supported the robustness and validity of the ITC results, with comparable OS and PFS between cemiplimab+PDC and pembrolizumab+PDC.
- 6.33 The ESC noted that the submission did not provide a non-inferiority margin.

Comparative harms

- 6.34 In Study 16113, the proportion of patients who experienced any treatment-emergent adverse events (TEAEs) was higher with cemiplimab+PDC when compared with placebo+PDC (RR of 1.02; 95% CI: 0.98, 1.06), with a greater difference in Grade ≥ 3 TEAEs events (1.49; 95% CI: 1.16, 1.92). The most frequently reported TEAEs (Grade ≥ 3) in cemiplimab+PDC arm were anaemia (10.9%) and neutropenia (6.4%).
- 6.35 In KN-189 and KN-407, the proportion of patients who experienced any AEs and Grade ≥ 3 AEs was higher in pembrolizumab+PDC arm when compared with placebo+PDC (RR of 1.08; 95% CI: 0.97, 1.21 and 1.07; 95% CI: 0.96, 1.18). The most frequently reported AEs (Grade ≥ 3) in pembrolizumab+PDC arm were anaemia and neutropenia in KN-189 (19.0% and 17.8%) and KN-407 (15.8% and 23.0%).
- 6.36 The submission presented an indirect comparison of adverse events based on all subjects as treated in Study 16113, KN-189 and KN-407. The results of ITC for safety outcomes are presented in Table 8.

Table 8: Summary of key adverse events in the trials

Trial type or estimate	Trial ID	PD-1 inhibitor+PDC n/N (%)	Placebo+PDC n/N (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
AEs regardless of attribution						
Cemiplimab+PDC vs. placebo+PDC	16113	301/312 (96.5%)	145/153 (94.8%)	1.51 (0.59, 3.83)	1.02 (0.98, 1.06)	0.02 (-0.02, 0.06)
Pembrolizumab+PDC vs. placebo+PDC	KN-189	404/405 (99.8%)	200/202 (99.0%)	4.04 (0.36, 44.82)	1.01 (0.99, 1.02)	0.01 (-0.01, 0.02)
	KN-407	274/278 (98.6%)	275/280 (98.2%)	1.25 (0.33, 4.69)	1.00 (0.99, 1.02)	0.00 (-0.02, 0.02)
	KN meta-analysis k=2				1.64 (0.51, 5.23)	1.01 (0.99, 1.02)
ITC cemiplimab+PDC vs. pembrolizumab+PDC	16113 vs. KN meta-analysis			0.92 (0.21, 4.09)	1.01 (0.96, 1.05)	0.01 (-0.04, 0.05)
AEs regardless of attribution (Grade 3-5)						

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Trial type or estimate	Trial ID	PD-1 inhibitor+PDC n/N (%)	Placebo+PDC n/N (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
Cemiplimab+PDC vs. placebo+PDC	16113	152/312 (48.7%)	50/153 (32.7%)	1.96 (1.31, 2.93)	1.49 (1.16, 1.92)	0.16 (0.07, 0.25)
Pembrolizumab+PDC vs. placebo+PDC	KN-189	295/405 (72.8%)	136/202 (67.3%)	1.30 (0.90, 1.88)	1.08 (0.97, 1.21)	0.06 (-0.02, 0.13)
	KN-407	208/278 (74.8%)	196/280 (70.0%)	1.27 (0.88, 1.85)	1.07 (0.96, 1.18)	0.05 (-0.03, 0.12)
	KN meta-analysis k=2			1.29 (0.99, 1.67)	1.07 (1.00, 1.16)	0.05 (0, 0.11)
ITC cemiplimab+PDC vs. pembrolizumab+PDC	16113 vs. KN meta-analysis			1.52 (0.94, 2.46)	1.39 (1.07, 1.82)	0.11 (0.01, 0.22)
AEs regardless of attribution leading to discontinuation						
Cemiplimab+PDC vs. placebo+PDC	16113	19/312 (6.1%)	7/153 (4.6%)	1.35 (0.56, 3.29)	1.33 (0.57, 3.10)	0.02 (-0.03, 0.06)
Pembrolizumab+PDC vs. placebo+PDC	KN-189	145/405 (35.8%)	35/202 (17.3%)	2.66 (1.75, 4.04)	2.07 (1.49, 2.87)	0.18 (0.11, 0.25)
	KN-407	48/278 (17.3%)	21/280 (7.5%)	2.57 (1.50, 4.43)	2.30 (1.42, 3.74)	0.10 (0.04, 0.15)
	KN meta-analysis k=2			2.63 (1.89, 3.66)	2.14 (1.63, 2.81)	0.14 (0.05, 0.23)
ITC cemiplimab+PDC vs. pembrolizumab+PDC	16113 vs. KN meta-analysis			0.51 (0.20, 1.33)	0.62 (0.26, 1.51)	-0.12 (-0.22, -0.03)
AEs regardless of attribution leading to discontinuation (Grade 3-5)						
Cemiplimab+PDC vs. placebo+PDC	16113	15/312 (4.8%)	4/153 (2.6%)	1.88 (0.61, 5.77)	1.84 (0.62, 5.45)	0.02 (-0.01, 0.06)
Pembrolizumab+PDC vs. placebo+PDC	KN-189	48/405 (11.9%)	14/202 (6.9%)	1.81 (0.97, 3.36)	1.71 (0.97, 3.03)	0.05 (0.00, 0.10)
	KN-407	34/278 (12.2%)	18/280 (6.4%)	2.03 (1.12, 3.69)	1.90 (1.10, 3.29)	0.06 (0.01, 0.11)
	KN meta-analysis k=2			1.92 (1.25, 2.95)	1.81 (1.22, 2.68)	0.05 (0.02, 0.09)
ITC cemiplimab+PDC vs. pembrolizumab+PDC	16113 vs. KN meta-analysis			0.98 (0.30, 3.25)	1.02 (0.32, 3.22)	-0.03 (-0.07, 0.02)
AEs regardless of attribution leading to death						
Cemiplimab+PDC vs. placebo+PDC	16113	27/312 (8.7%)	14/153 (9.2%)	0.94 (0.48, 1.85)	0.95 (0.51, 1.75)	-0.005 (-0.06, 0.05)
Pembrolizumab+PDC vs. placebo+PDC	KN-189	29/405 (7.2%)	14/202 (6.9%)	1.04 (0.53, 2.01)	1.03 (0.56, 1.91)	0.00 (-0.04, 0.05)
	KN-407	32/278 (11.5%)	20/280 (7.1%)	1.69 (0.94, 3.04)	1.61 (0.95, 2.75)	0.04 (0, 0.09)
	KN meta-analysis k=2			1.36 (0.84, 2.19)	1.33 (0.86, 2.04)	0.02 (-0.02, 0.06)
ITC cemiplimab+PDC vs. pembrolizumab+PDC	16113 vs. KN meta-analysis			0.69 (0.30, 1.58)	0.71 (0.34, 1.51)	-0.02 (-0.09, 0.04)
Immune AEs (Grade 3-5)						
Cemiplimab+PDC vs. placebo+PDC	16113	14/312 (4.6%)	0/153 (0%)	14.89 (0.88, 251.29)	14.27 (0.86, 237.61)	0.04 (0.02, 0.07)
Pembrolizumab+PDC vs. placebo+PDC	KN-189	52/405 (12.8%)	9/202 (4.5%)	3.16 (1.52, 6.55)	2.88 (1.45, 5.73)	0.08 (0.04, 0.13)
	KN-407	37/278 (13.3%)	9/280 (3.2%)	4.62 (2.19, 9.78)	4.14 (2.04, 8.42)	0.10 (0.06, 0.15)

Trial type or estimate	Trial ID	PD-1 inhibitor+PDC n/N (%)	Placebo+PDC n/N (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
	KN meta-analysis k=2			3.80 (2.26, 6.41)	3.43 (2.10, 5.63)	0.09 (0.06, 0.12)
ITC cemiplimab+PDC vs. pembrolizumab+PDC	16113 vs. KN meta-analysis			3.92 (0.22, 69.36)	4.16 (0.0, 5077.8)	-0.05 (-0.09, -0.01)

Source: Table 2-25, pp60-61 of the submission.

AE = adverse events; CI = confidence interval; ITC = indirect treatment comparison; ITT = intention-to-treat; k = number of studies contributing to the pooled estimate of effect; n = number of participants reporting data; N = total participants in group; OR = odds ratio; PDC = platinum doublet chemotherapy PD-L1 = programmed cell death ligand 1; RD = risk difference; RR = relative risk.

Bold indicates statistical significance.

6.37 The risk of any AEs was similar between cemiplimab+PDC and pembrolizumab+PDC. However, there were statistically significant differences in the indirect RR and RD for AEs Grade \geq 3, favouring pembrolizumab+PDC. In contrast, there were statistically significant differences in the indirect RD for AEs leading to discontinuation and immune AEs, favouring cemiplimab+PDC. This difference was not seen in RR and OR. The wide 95% confidence intervals for most of the indirect estimates of treatment effects suggest that the ITC of AEs was statistically underpowered.

6.38 Of note, the PBAC has previously considered that the safety profiles of PD-L1 inhibitors are likely to be similar (para 7.9, Cemiplimab, PSD, November 2021 PBAC Meeting).

Benefits/harms

6.39 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

6.40 The submission described cemiplimab+PDC as non-inferior in terms of effectiveness compared to pembrolizumab+PDC. The evaluation considered the claim was adequately supported by evidence, but the following issues need to be considered:

- The effectiveness of cemiplimab+PDC in patients with PD-L1 $<$ 1% remained uncertain due to a lower median OS reported in the cemiplimab+PDC arm (12.8 months) compared to the placebo+PDC arm (14.2 months) in the primary analysis of Study 16113, with a HR of 1.006 (95% CI: 0.63, 1.60). The results from the final analyses also did not support the claim of superior efficacy in patients with PD-L1 $<$ 1%, with a HR for OS of 0.94 (95% CI: 0.62, 1.42). The Pre-Sub-Committee Response (PSCR) argued that the OS hazard ratio (HR) point estimate in this subgroup improved from 1.006 to 0.94 in the final analysis (data cut-off: June 2022) and that there was no biological plausibility to suggest a worsening survival benefit in patients with PD-L1 $<$ 1% given the improved PFS (HR: 0.73; 95% CI: 0.50, 1.08) when compared to placebo+PDC. The ESC did not consider the efficacy in patients with PD-L1 $<$ 1% to be a key issue for the PBAC to consider.
- Transitivity issues across the trials in terms of stratification factors, histology, disease stage, gender, ECOG performance status, presence of brain metastases at

diagnosis, affect the transitivity assumption that forms the basis of ITC between cemiplimab+PDC and pembrolizumab+PDC.

- The submission did not present any MAIC to adjust for the heterogeneities in the baseline characteristics and demographics.
 - The submission did not provide a non-inferiority margin.
- 6.41 The submission described cemiplimab+PDC as non-inferior in terms of safety compared to pembrolizumab+PDC.
- 6.42 The ESC considered that while the clinical claim was reasonably well supported, a MAIC would have been informative to account for transitivity issues with the ITC.
- 6.43 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.44 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.45 The submission presented a cost-minimisation approach (CMA) based on the indirect comparison between cemiplimab+PDC to pembrolizumab+PDC using placebo+PDC as the common reference for patients with Stage IV NSCLC.
- 6.46 The equi-effective doses were estimated as cemiplimab 350 mg Q3W administered as an IV infusion over 30 minutes plus PDC administered as an IV infusion and pembrolizumab 200 mg Q3W administered as an IV infusion over 30 minutes plus PDC administered as an IV infusion, assuming the same treatment durations and dose intensities.
- 6.47 Table 9 summarises the data cut-off and median follow-up duration of Study 16113, KN-189 and KN-407 used by the submission to determine duration of treatment in the CMA. The submission compared the results of KN-189 (median follow-up of 23.1 months; data cut-off September 2018) and KN-407 (median follow-up of 14.3 months; data cut-off: May 2019) at data cut-offs that provide the most similar length of follow-up to that of Study 16113 (median follow-up of 16.4 months; data cut-off: June 2021). This approach was inconsistent with the approach taken in the clinical evaluation, which utilised results of Study 16113 from the recent cut-off date (median follow-up of 28.4 months; data cut-off; June 2022). The results of Study 16113 from the June 2022 data cut-off are more closely aligned with those of KN-189 from either the September 2018 or May 2019 data cut-offs, given the similar median follow-up durations (28.4 months vs 23.1 or 31 months).
- 6.48 The submission assumed the mean duration of treatment to be similar between cemiplimab (10.5 months in Study 16113) and pembrolizumab (9.8 months in KN-189). Mean duration of treatment was not reported for KN-407; however, a difference was

observed in the median treatment duration between cemiplimab (9.7 months) and pembrolizumab (7.1 months in KN-407).

Table 9: Duration of treatment of cemiplimab+PDC and pembrolizumab+PDC

Factor	Cemiplimab+PDC Study 16113 (used in clinical evaluation) ^a	Cemiplimab+PDC Study 16113 (used in economic evaluation)	Pembrolizumab+PDC KN-189 (NSQ)	Pembrolizumab+PDC KN-407 (SQ)
Median follow-up in treatment arm	28.4 months	16.4 months	23.1 months	14.3 months
Data cut-off date	14 June 2022	14 Jun 2021	21 Sep 2018	9 May 2019
Mean duration of treatment (SD) (months)	12.3	10.5 (6.4)	9.8 (7.8)	Not reported
Median duration of treatment (months)	9.0	9.7	Not reported	7.1
Treatment ongoing at median follow-up, n/N (%)	20/312 (6.4%)	108/312 (34.6%)	58/616 (14.1%)	40/278 (14.4%)

Source: Table 3-3, p88 of the submission.

n = number of participants reporting data; N = total participants in group; NSQ = non-squamous; PDC = platinum doublet chemotherapy; SD = standard deviation; SQ = squamous.

^a Makharadze et al, 2023

- 6.49 Given high utilisation of pembrolizumab (200 mg Q3W; 92%) as per PBS and RPBS items processed, the submission considered cemiplimab+PDC (350 mg Q3W) was unlikely to substitute for pembrolizumab (400 mg Q6W) to a significant extent. This was consistent with approach used for CMA in cemiplimab monotherapy for Stage IV NSCLC (paragraph 6.38, cemiplimab, PSD, November 2021 PBAC meeting). The use of pembrolizumab 200 mg Q3W and 400 mg Q6W was tested in the sensitivity analyses conducted during the evaluation.
- 6.50 The equi-effective doses did not account for differences in relative dose intensity (RDI), as the dosing intensity data were missing from the KN studies.
- 6.51 The submission excluded the costs of chemotherapy in the CMA for both cemiplimab+PDC and pembrolizumab+PDC, assuming that the type and number of courses of chemotherapy would not differ between the two arms. This was reasonable given that the number of doses for chemotherapy and chemotherapy regimen was largely similar across the studies.
- 6.52 The submission did not include the cost of conducting PD-L1 test (MBS Item: 72814) given that the test is conducted once for every new patient diagnosed with NSCLC to determine the choice of therapy and the PBS listing of cemiplimab+PDC was not expected to change the clinical practice or increase the utilisation of the test. This was reasonable and consistent with cemiplimab monotherapy for Stage IV (metastatic) NSCLC (paragraph 6.41, cemiplimab, PSD, November 2021 PBAC meeting).
- 6.53 The submission also excluded the cost of adverse events based on the assumption that the safety profiles of cemiplimab+PDC and pembrolizumab+PDC are non-inferior. This was reasonable given that the safety profiles of PD-L1 inhibitors are likely to be similar.

6.54 The results of the CMA are summarised in Table 10.

Table 10: Result of cost-minimisation approach using effective prices

Component	Cemiplimab 350 mg	Pembrolizumab 200 mg
Drug cost (ex-manufacturer price) per administration		
Dose per administration	350 mg	200 mg
Vials required per administration (mg)	1 (350 mg)	2 (100 mg)
Effective AEMP per vial	\$ ^a	\$
Effective AEMP per administration	\$	\$
Equi-effective dose		
Administration per Q3W	1	1
Equi-effective dose per Q3W	350 mg	200 mg
Drug cost (ex-manufacturer price) Q3W at equi-effective dose		
Total drug costs per Q3W	\$	\$
Total incremental cost per Q3W		\$

Source: Table 3-4, p90 of the submission.

AEMP = approved ex-manufacturer price; Q3W = every three weeks.

a The current AEMP for cemiplimab for the treatment of NSCLC.

- 6.55 The submission stated that an effective price of \$ [REDACTED] for a 350 mg cemiplimab vial will provide the same cost per administration to pembrolizumab 200 mg, at its effective price (equivalent to 2 × \$ [REDACTED] for 100 mg vial). The submission assumed that the effective price of pembrolizumab when used in combination with chemotherapy was same as that of pembrolizumab monotherapy, given the broad PBS listing of pembrolizumab for Stage IV NSCLC.
- 6.56 Based on the updated analysis for cemiplimab (data cut-off: June 2022), the mean duration of treatment was approximately 12.3 months (53.34 weeks). A longer mean duration of treatment with cemiplimab+PDC compared to pembrolizumab+PDC would result in a higher treatment cost if the CMA was based on equivalent per cycle cost.
- 6.57 Sensitivity analyses have been conducted as a part of the evaluation to establish that the cost per patient for treatment with cemiplimab+PDC would be no more than the cost per patient for treatment with pembrolizumab+PDC using the longer duration of treatment for cemiplimab+PDC (data cut-off: June 2022). The results of the sensitivity analyses are presented in Table 11.

Table 11: Results of sensitivity analyses

Component	Cemiplimab+PDC	Pembrolizumab+PDC	
Base case			
Effective AEMP	\$	\$	
Using the mean treatment duration from Study 16113 (12.3 months) from the recent data-cut off (June 2022)			
Effective AEMP	\$ ^a	\$	
Cycles ^b	17.780	14.155	
Total cost of treatment	\$	\$	
Using the mean treatment duration from the Study 16113 (12.3 months) and the cost of IV administration^c			
Effective AEMP	\$ ^a	\$	
Cycles	17.780	14.155	
Total drug cost	\$	\$	
Total cost of IV administration	\$2,103.37	\$1,674.60	
Total cost of treatment	\$	\$	
Using the mean treatment duration from the Study 16113 (12.3 months) the cost of IV administration^c, and weighted utilisation of pembrolizumab 200 mg Q3W (92%) and 400 mg Q6W (8%)			
Effective AEMP	350 mg Q3W	200 mg Q3W	400 mg Q6W
	\$ ^a	\$	\$
Cycles	17.780	14.155	7.077
Total drug cost	\$	\$	\$
Total cost of IV administration	\$2,103.37	\$1,674.60	\$837.30
Total cost of treatment	\$	\$	\$
Weighted utilisation	-	92%	8%
Weighted total cost of treatment	\$	\$	

Source: Calculated during evaluation.

AEMP = approved ex-manufacture price; Q3W = every three weeks; Q6W = every six weeks; IV = intravenous; PDC = platinum-doublet chemotherapy.

^a Effective AEMP for cemiplimab were back calculated assuming the total cost of treatment with cemiplimab+PDC would be no more than that of pembrolizumab+PDC

^b No. of cycles (Q3W) = (Mean duration of treatment/12) * (52/3) or Mean duration of treatment (weeks)/3.

^c Includes the cost of IV administration (MBS Item 13950 = \$118.30) given the difference in treatment duration.

- 6.58 The sensitivity analyses showed that using the 12.3 months duration of treatment from the recent data cut-off (June 2022) of Study 16113, lowered the cost for cemiplimab from \$ to \$. When weighted utilisation for pembrolizumab (200 mg Q3W and 400 mg Q6W) was used, there was a slight further reduction. The pre-PBAC response argued that the number of doses administered is the most appropriate comparison, with the mean number of doses being 13.4 for cemiplimab study and 12.6 for the pembrolizumab trials. The pre-PBAC response also asserted that it was reasonable to assume the treatment duration to be the same for cemiplimab and pembrolizumab, given the similarities in the intended duration of treatment (maximum of 24 months or 35 cycles).
- 6.59 The ESC considered that the difference in mean duration of treatment highlighted the transitivity issues between the studies, reflecting different patient populations in the cemiplimab and pembrolizumab studies.
- 6.60 The ESC considered that the treatment duration of cemiplimab is likely to be the same as for pembrolizumab when it is used in the same patient population, and that the observed difference in treatment duration may reflect differences in the patient populations in the clinical trials.

- 6.61 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 cemiplimab+PDC would be no more than the cost per patient of pembrolizumab+PDC. 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. In this case, the PBAC should consider the following parameters: duration of treatment.
- 6.62 The ESC considered that in the absence of a MAIC, the financial risk to the Government of the treatment duration for cemiplimab being longer than that for pembrolizumab could be mitigated through a price reduction for cemiplimab that was informed by calculation of the cost-minimised price of cemiplimab being based on the treatment duration for cemiplimab of 12.3 months (based on the latest data cut), being equivalent to 9.8 months of pembrolizumab. The pre-PBAC response argued that the shorter duration of treatment in the pembrolizumab trials was likely because of higher rates of adverse events in the KEYNOTE trials, leading to discontinuation of the treatment. The pre-PBAC response maintained that that the non-inferiority claim was well supported, and that the cost-minimisation approach appropriately assumed the same treatment duration for cemiplimab and pembrolizumab at price parity with an effective vial price of \$ 1. The pre-PBAC response further argued that any residual uncertainty should be accounted for through the standard 24-month Drug Utilisation Sub-Committee (DUSC) review.

Drug cost/patient/course

- 6.63 Based on the weighted effective DPMA of \$ 1, the mean cost for a patient receiving cemiplimab+PDC is \$ 1. This is based on a mean duration of treatment of 12.3 months (53.34 weeks) observed in the cemiplimab+PDC arm from Study 16113, with 6.4% of patients still receiving cemiplimab+PDC treatment (data cut-off: June 2022).

Estimated PBS usage & financial implications

- 6.64 This submission was not considered by DUSC. The submission used a market share approach to estimate the utilisation and financial impact of listing cemiplimab+PDC for the treatment of patients with Stage IV NSCLC.
- 6.65 Table 12 summarises the key inputs and data sources to estimate the financial impact.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Predicted annual growth rate of pembrolizumab prescriptions for the treatment of Stage IV NSCLC patients	Predicted growth rate of 18% in Year 2024 decreasing to 9% in Year 2029; based on trendline equations to forecast annual growth rate based on historical Services Australia data for pembrolizumab (2018 to 2022).	This was likely overestimated; the overall NSCLC market was considered to be stable by the DUSC, with a decline in immunotherapies (Public Release Document, September 2022 DUSC Meeting). However, the submission estimated a growth rate of 45% in 2023, which is likely to be overestimated.
Proportion of Stage IV NSCLC patients who would use pembrolizumab+PDC	70% of pembrolizumab prescriptions would be used by patients in combination with PDC; this was based on the previous PBAC consideration of cemiplimab where close to 30% of patients were assumed to use pembrolizumab as monotherapy (para 6.46, Cemiplimab, Public Summary Document, November 2021 PBAC Meeting).	This was reasonable and consistent with the PBAC consideration of cemiplimab monotherapy.
Uptake rate of cemiplimab+PDC	2% in Year 1 increasing to 10% in Year 6; based on the sponsor's assumption and was also used during the PBAC consideration of cemiplimab monotherapy.	This was uncertain; the submission did not consider the availability of other drugs listed on the PBS for the treatment of Stage IV NSCLC.

Source: Table 4-2, p93 of the submission.

DUSC = drug-utilisation sub-committee; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy.

6.66 The estimated use and financial implications of listing cemiplimab+PDC are presented in Table 13.

Table 13: Estimated use and financial implications using effective prices

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of prescriptions dispensed ^a	1	1	1	1	5	5
Estimated financial implications of cemiplimab+PDC						
Cost to PBS/RPBS less co-payments	2	2	2	4	4	4
Estimated financial implications for pembrolizumab+PDC						
Cost to PBS/RPBS less co-payments	3	3	3	3	3	3
Net financial implications						
Net cost to PBS/RPBS	2	2	2	2	2	2
Net cost to MBS	2	2	2	2	2	2
Net cost to PBS/RPBS/MBS	2	2	2	2	2	2

Source: Table 4-18, p102 and Table 4-21, p103 of the submission

PDC = platinum doublet chemotherapy; MBS = Medicare Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Assuming the uptake rate of 2% in Year 1 increasing to 10% by Year 6 as estimated by the submission.

Corrected during evaluation using the new prices for Efficient Funding of Chemotherapy as of 1 July 2023 and corrected number of prescriptions for pembrolizumab+PDC.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² \$0 to < \$10 million

³ net cost saving

⁴ \$10 million to < \$20 million

⁵ 5,000 to < 10,000

6.67 There were some uncertainties regarding the key assumptions used to determine the projected utilisation of cemiplimab+PDC:

- The projected annual growth rate for pembrolizumab was likely overestimated, with approximately 45% in 2023, 18% in Year 1 decreasing to 9% in Year 6. In September 2022, DUSC considered the overall NSCLC market to be stable and noted that over time, utilisation of immunotherapies has been declining, whilst utilisation of targeted therapies has been increasing (Public Release Document, September 2022 DUSC Meeting). The PSCR stated that given that a market share approach was used, the financial implication of direct substitution of cemiplimab + PDC at price parity to pembrolizumab + PDC will not be impacted by the market growth rate.
 - The assumed uptake rate of 2% in Year 1 increasing to 10% in Year 6 for cemiplimab+PDC was uncertain given the availability of other drugs listed on the PBS (pembrolizumab monotherapy, cemiplimab monotherapy, atezolizumab in combination with bevacizumab and PDC, nivolumab in combination with ipilimumab and PDC) for the treatment of Stage IV NSCLC.
- 6.68 However, 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 incremental cost to the PBS/RPBS/MBS.
- 6.69 The submission did not account for differences in utilisation of chemotherapy, cost of administering IV, cost of PD-L1 test, or differences in adverse event profiles, as these were not expected to differ between the two treatments. This may be reasonable.

Quality Use of Medicines

- 6.70 The submission stated that support materials will be developed and disseminated for clinicians to explain the benefits and risks associated with cemiplimab treatment, as well as for patients to understand their diagnosis and provide information on cemiplimab treatment, including potential side effects.

Financial Management – Risk Sharing Arrangements

- 6.71 The submission stated that the sponsor is amenable to joining the current risk sharing arrangements applying to PD-L1 inhibitors 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 to be used with platinum doublet chemotherapy (PDC) as a first-line treatment of adult patients with Stage IV (metastatic) non-small cell lung cancer (NSCLC) with no evidence of epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or c-ROS-proto-oncogene 1 (ROS1) aberrations. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of

cemiplimab plus PDC would be acceptable if it were cost-minimised to pembrolizumab plus PDC.

- 7.2 The PBAC did not consider there to be an unmet clinical need for cemiplimab, as there are currently multiple PBS listed immunotherapies to treat patients with stage IV NSCLC. However, the PBAC noted the consumer comments regarding the benefit of having an alternative treatment option available to patients.
- 7.3 The PBAC noted that at its meeting in November 2021, it recommended the listing of cemiplimab for patients with Stage IV (metastatic) NSCLC who expressed PD-L1 in $\geq 50\%$ tumour cells on a cost-minimisation basis to pembrolizumab.
- 7.4 The PBAC considered that the nominated main comparator of pembrolizumab+PDC was appropriate.
- 7.5 The PBAC noted the submission was based on an indirect treatment comparison (ITC) of one randomised cemiplimab trial (Study 16113), which compared cemiplimab+PDC with placebo+PDC; and two randomised pembrolizumab trials (KN-189 and KN-407), which compared pembrolizumab+PDC with placebo+PDC. The PBAC considered that the ITC showed there was no significant difference in overall survival (OS) and progression free survival (PFS) between cemiplimab+PDC and pembrolizumab+PDC (OS HR: 1.00; 95% CI: 0.75, 1.34 and PFS HR: 0.98; 95% CI: 0.72, 1.33). The PBAC noted heterogeneity between the trials in terms of age, gender, region, smoking status, ECOG-PS, brain metastasis, PD-L1 expression, disease at baseline and histology, which may impact interpretation of the indirect treatment comparison. However, the PBAC agreed with the pre-PBAC Response that the bias could be in either direction. The PBAC also noted that a non-inferiority margin was not proposed. Further, the Committee agreed with the ESC that a matching adjusted indirect comparison would have been a better approach to address the transitivity issues. However, the PBAC noted that similar issues were seen with the previous submission of cemiplimab monotherapy versus pembrolizumab for PD-L1 expression $\geq 50\%$, and considered that the risk of uncertainties arising from the ITC would be minimal. Overall, the PBAC considered that the claim of non-inferior effectiveness of cemiplimab+PDC compared to pembrolizumab+PDC was supported.
- 7.6 The PBAC noted that the risk of any adverse events was similar between cemiplimab+PDC and pembrolizumab+PDC, although the ITC of adverse events was statistically underpowered. The PBAC, however, considered that the safety profile of PD-L1 inhibitors were likely to be similar, and therefore it was reasonable to conclude that cemiplimab+PDC was non-inferior in terms of safety compared to pembrolizumab+PDC.
- 7.7 The PBAC considered that the economic model was appropriate, however, noted that the economic model assumed the same treatment duration, whereas the mean duration of treatment between the cemiplimab trial and KN studies (12.3 months in Study 16113 and 9.8 months in KN-189) was different when a different data cut-off was applied (paragraph 6.63). The PBAC considered that the difference in the mean

duration of treatment may reflect differences in the patient populations in the clinical trials and that the treatment duration would likely be the same when the treatments were used in the same patient populations.

- 7.8 The PBAC noted the CMA presented in the submission was conducted over one 3-week treatment cycle. The PBAC noted pembrolizumab could be administered as 200 mg Q3W or 400 mg Q6W but considered that given the high utilisation of pembrolizumab 200 mg Q3W that cemiplimab+PDC (350 mg Q3W) was unlikely to substitute for pembrolizumab (400 mg Q6W) to a significant extent, and that it was reasonable to base the CMA on the pembrolizumab Q3W dose regimen.
- 7.9 The PBAC advised that the equi-effective doses are cemiplimab 350 mg Q3W plus PDC and pembrolizumab 200 mg Q3W plus PDC.
- 7.10 The PBAC noted that the assumption of market growth of 18% in Year 1 decreasing to 9% in Year 6 was overestimated given that use of immunotherapies has been stable over the recent years. The PBAC considered that the uptake would likely be 2% in Year 1 increasing to 5% to 10% in Year 6. However, the PBAC considered that, at a price cost-minimised to the effective price of pembrolizumab, the listing of cemiplimab+PDC on the PBS for patients with NSCLC would be expected to result in no additional cost to the PBS/RPBS.
- 7.11 The PBAC considered it would be appropriate for cemiplimab (for first line use in combination with PDC) to join the current risk sharing arrangements applying to PD-L1 inhibitors for the treatment of NSCLC with no increase to the current expenditure caps.
- 7.12 The PBAC considered that a combined listing for cemiplimab 350 mg as a monotherapy or in combination with PDC in Stage IV NSCLC was reasonable. The PBAC noted that the wording of the proposed PBS restriction for cemiplimab was similar to the listing of pembrolizumab for the treatment of Stage IV NSCLC.
- 7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because cemiplimab+PDC 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.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Amend existing listing as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
CEMIPLIMAB Injection	13169D (Public) MP 13160P (Private) MP	350 mg	6	Sanofi Aventis Australia Pty Ltd
Available brands				
Libtayo (cemiplimab 350 mg/7 mL injection, 7 mL vial)				
Restriction Summary [new 1] Treatment of concepts [new 2]				
Category / Program: Section 100 – Efficient Funding of Chemotherapy - Public and Private Hospitals				
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined (ST code: new 2)				
Administrative Advice: No increase in the maximum amount or number of units may be authorised.				
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.				
Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)				
Treatment Phase: Initial treatment – 3 weekly treatment regimen				
Clinical criteria:				
Patient must not have previously been treated for this condition in the metastatic setting; OR				
The condition must have progressed after treatment with tepotinib,				
AND				
Clinical criteria:				
Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for non-small cell lung cancer,				
AND				
Clinical criteria:				
Patient must have a WHO performance status of 0 or 1,				
AND				
Clinical criteria:				
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				
Clinical criteria:				

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	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
	Clinical criteria:
	The treatment must be the sole PBS subsidised systemic anti-cancer therapy for this condition
	AND
	Clinical criteria:
	The treatment must not exceed a total of 7 doses under this restriction.

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Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
CEMIPLIMAB	13161Q (Public) MP 13162R (Private) MP	350 mg	6	Sanofi Aventis Australia Pty Ltd
Available brands				
Libtayo cemiplimab 350 mg/7 mL injection, 7 mL vial)				
Restriction Summary [new 3] Treatment of concepts [new 4]				
Concept ID	Category / Program: Section 100 – Efficient Funding of Chemotherapy - Public and Private Hospitals			
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined (ST code: new 4)			
	Administrative Advice: No increase in the maximum amount or number of units may be authorised.			
	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.			
	Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC)			
	Treatment Phase: Continuing treatment – 3 weekly treatment regimen			
	Clinical criteria: Patient must have previously received PBS subsidised treatment with this drug for this condition,			
	AND			
	Clinical criteria: Patient must not have developed disease progression while being treated with this drug for this condition,			
	AND			
	Clinical criteria: The treatment must be the sole PBS subsidised systemic anti-cancer therapy for this condition			
	AND			
	Clinical criteria: 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.			

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.