

**6.01 ATEZOLIZUMAB,
solution concentrate for I.V. infusion 1200 mg in
20 mL,
Tecentriq[®],
plus
BEVACIZUMAB,
solution concentrate for I.V. infusion 100 mg in 4 mL,
solution concentrate for I.V infusion 400 mg in 16 mL,
Avastin[®],
Roche Products Pty Ltd.**

1 Purpose of application

- 1.1 Section 100 (Efficient Funding of Chemotherapy) Authority Required (Streamlined) listing for both atezolizumab and bevacizumab, for use in combination, in addition to platinum doublet chemotherapy (PDC), for the treatment of patients with metastatic non-squamous (NSQ) non-small cell lung cancer (NSCLC). Atezolizumab in combination with bevacizumab and PDC has not been considered by the PBAC for this indication previously.
- 1.2 The requested listing was based on a cost-utility analysis of atezolizumab + bevacizumab + PDC compared with PDC and a cost-minimisation analysis against 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 metastatic non-squamous NSCLC (with or without oncogenic drivers).
Intervention	<u>Induction</u> : atezolizumab (1,200 mg) + bevacizumab (15 mg/kg) + platinum-doublet chemotherapy for 4-6, 21 day cycles. <u>Maintenance</u> : atezolizumab (1,200 mg) + bevacizumab (15 mg/kg) every 21 days until loss of clinical benefit ^a (atezolizumab) and/or progression (bevacizumab)
Comparator	Main comparator: platinum-doublet chemotherapy. Supplementary comparator for EGFR wild type/ALK negative, PD-L1 high population: pembrolizumab monotherapy.
Outcomes	Overall survival, progression-free survival, objective response rate, duration of response, safety
Clinical claim	Atezolizumab + bevacizumab ^b has superior efficacy and inferior safety to platinum-doublet chemotherapy.

ALK anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death ligand 1.

^a Defined in the proposed PBS restriction for atezolizumab as patients who no longer have stable or responding disease.

^b Atezolizumab and bevacizumab in combination with platinum-doublet chemotherapy.

Source: Table ES.1, p2 of the submission

- 1.3 The submission identified two sub-populations of patients with NSQ NSCLC:
- i) Patients whose tumours demonstrate no evidence of either activating mutations of the epidermal growth factor receptor (EGFR) gene mutation or an anaplastic lymphoma kinase (ALK) gene rearrangement (EGFR wildtype/ALK negative population), in whom atezolizumab + bevacizumab + PDC was proposed as a first-line treatment option, and
 - ii) Patients whose tumours have evidence of either activating EGFR mutations or ALK gene rearrangements (EGFR mutant/ALK positive population), in whom atezolizumab + bevacizumab + PDC was proposed as a later-line treatment option, after targeted therapy with at least one tyrosine kinase inhibitor (TKI).

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

2 Requested listings

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing criteria are added in italics and suggested deletions are crossed out with strikethrough.
- 2.2 The submission requested separate listings for the EGFR wild type/ALK negative population and the EGFR mutant/ALK positive population.

Atezolizumab

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
ATEZOLIZUMAB 1,200 mg/20 mL injection, 1 x 20 mL vial	1,200 mg	Initial: 5 Continuing:7	Published price: \$7,704.63 (private) \$7,560.74 (public) Effective price \$ [REDACTED] (private) \$ [REDACTED] (public)	Tecentriq Roche Products Pty Ltd

EGFR wild type/ALK negative NSQ NSCLC

Category / Program	Section 100 – Efficient funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
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) previously untreated
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) previously untreated non-small cell lung cancer NSCLC
Treatment phase:	Initial treatment

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Restriction Level / Method:	<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
Treatment criteria:	<i>Patient must be undergoing combination treatment with bevacizumab and platinum-doublet chemotherapy.</i>
Clinical criteria:	<p>The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, AND Patient must not have been treated for this condition in the metastatic setting, AND Patient must have a WHO performance status of 0 or 1 or less, AND The treatment must be in combination with bevacizumab and platinum-doublet chemotherapy. <i>The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation or an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.</i></p>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised.</p> <p>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><i>Special pricing arrangements apply</i></p>

EGFR mutant type/ALK positive NSQ NSCLC

Category / Program	Section 100 – Efficient funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
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-squamous Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) non-small cell lung cancer-NSCLC
Treatment phase:	Initial treatment
Restriction Level / Method:	<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
Treatment criteria:	<i>Patient must be undergoing combination treatment with bevacizumab and platinum-doublet chemotherapy.</i>

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<p>Clinical criteria:</p>	<p>The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, AND Patient must have a WHO performance status of 0 or 1 or less, AND <i>Patient must have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation or of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.</i> AND The treatment must be in combination with bevacizumab and platinum-doublet chemotherapy, AND Patient must have progressive disease following treatment with an epidermal growth factor receptors (EGFR) OR anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKI), 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 this condition.</p>
<p>Administrative Advice</p>	<p>Patient must have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation or of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.</p> <p>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>No increase in the maximum number of repeats may be authorised.</p> <p><i>Special pricing arrangements apply</i></p>

Bevacizumab

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
BEVACIZUMAB 100 mg/4 mL injection 400 mg/16 mL injection	1,800 mg 2 x 100 mg vials, 4 x 400 mg vials	Initial: 5 Continuing:7	Published price: \$7,579.60 (private) \$7,437.44 (public) Effective price* \$ [REDACTED] (private) \$ [REDACTED] (public)	Avastin Roche Products Pty Ltd

EGFR wild type/ALK negative NSQ NSCLC

<p>Category / Program</p>	<p>Section 100 – Efficient funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)</p>
<p>Prescriber type:</p>	<p><input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives</p>

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Severity:	Stage IV (metastatic) previously untreated
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) previously untreated non-small cell lung cancer NSCLC
Treatment phase:	Initial treatment
Restriction Level / Method:	<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
Treatment criteria:	<i>Patient must be undergoing combination treatment with atezolizumab and platinum-doublet chemotherapy.</i>
Clinical criteria:	<p>The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC,</p> <p>AND</p> <p>Patient must not have been treated for this condition in the metastatic setting,</p> <p>AND</p> <p>Patient must have a WHO performance status of 0 or 1-1 or less,</p> <p>AND</p> <p><i>The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation or an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.</i></p>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised.</p> <p><i>Special pricing arrangements apply.</i></p>

EGFR mutant type/ALK positive NSQ NSCLC

Category / Program	Section 100 – Efficient funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
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-squamous Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) non-small cell lung cancer NSCLC
Treatment phase:	Initial treatment
Restriction Level / Method:	<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
Treatment criteria:	<i>Patient must be undergoing combination treatment with atezolizumab and platinum-doublet chemotherapy.</i>

<p>Clinical criteria:</p>	<p>The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, AND Patient must have a WHO performance status of 0 or 1 or less, AND <i>Patient must have evidence of an activating epidermal growth factor receptor (EGFR) gene or of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.</i> AND Patient must have progressive disease following treatment with epidermal growth factor receptors (EGFR) OR anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKI), 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 this condition</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised. <i>Special pricing arrangements apply</i></p>

- 2.3 The submission proposed a special pricing arrangement (SPA), with a [REDACTED] % rebate on the ex-manufacturer price for atezolizumab, and a [REDACTED] rebate on the ex-manufacturer price of bevacizumab when used in combination with atezolizumab for the treatment of metastatic NSCLC. The Pre-PBAC response offered a revised [REDACTED] % rebate on the ex-manufacturer price of atezolizumab via a SPA.
- 2.4 The requested restrictions allow the use of atezolizumab and bevacizumab in combination with any PDC regimen.

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

3 Background

Registration status

- 3.1 **TGA status at time of PBAC consideration:** The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Delegate’s Overview was available.
- 3.2 The TGA Delegate’s Overview was supportive of approving atezolizumab in combination with paclitaxel and carboplatin and bevacizumab for the first-line treatment of patients with metastatic NSQ NSCLC.
- 3.3 Bevacizumab is TGA registered for the following indication: bevacizumab, in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous NSCLC. Bevacizumab is not specifically registered for use in combination with atezolizumab.

Previous PBAC consideration

- 3.4 The PBAC has not previously considered atezolizumab and bevacizumab for use in combination, in addition to PDC, for this condition.

4 Population and disease

- 4.1 In Australia, lung cancer is the leading cause of cancer death, representing 18.8% of all cancer deaths in 2016 (8,839 deaths). NSCLC represents the main histological type of lung cancer, accounting for approximately 85% of lung cancer cases, and can be categorised into two histologic subtypes: squamous and non-squamous. Due to early-stage lung cancer being largely insidious, it is estimated that greater than 50% of patients have metastatic (Stage IV) disease at diagnosis, with the most common metastatic sites being bone, lungs, brain, liver and adrenal glands. The overall five-year survival rate is 14.3%. The Pre-Sub-Committee Response (PSCR) stated that enrolment of ■ patients in the medicines assistance access program since July 2018 indicated the unmet need and clinician support for this treatment in these populations, noting enrolment is approximately 50% across the two patient sub-populations (with and without oncogenic drivers).
- 4.2 Atezolizumab + bevacizumab + PDC was proposed as an alternative first line treatment option in patients with EGFR wild type/ALK negative Stage IV NSQ NSCLC, and as a later-line treatment option following one or more targeted therapies in patients with EGFR mutant/ALK positive Stage IV NSCLC.

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

5 Comparator

- 5.1 The submission nominated PDC as the main comparator but acknowledged that the combination of atezolizumab + bevacizumab + PDC would replace the sequential use of PDC followed by cancer immunotherapy. The PSCR stated that the submission appropriately considered the main comparator to be PDC followed by subsequent cancer immunotherapy, which was presented in the economic and financial models, the relevant algorithm and the best available data for comparison of atezolizumab + bevacizumab + PDC to sequential use of PDC followed by cancer immunotherapy.
- 5.2 The ESC considered the sequential use of PDC followed by a PD-(L)1 inhibitor may be the most appropriate comparator in the majority of patients, with the exception of those with EGFR wild type/ALK negative NSQ NSCLC with high PD-L1 expression. The ESC noted that while there is limited data on the use of PD-(L)1 inhibitors post TKI treatment, nivolumab and atezolizumab can be used in patients who have progressed on or after treatment with targeted therapies and sequential use of PDC followed by cancer immunotherapy could also be considered an appropriate comparator.
- 5.3 Pembrolizumab monotherapy was nominated as a supplementary comparator in patients with EGFR wild type/ALK negative NSQ NSCLC with high PD-L1 expression.

The ESC considered that pembrolizumab monotherapy, the only PD-(L)1 currently PBS listed for this indication, followed by PDC was the appropriate main comparator in this patient subgroup.

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

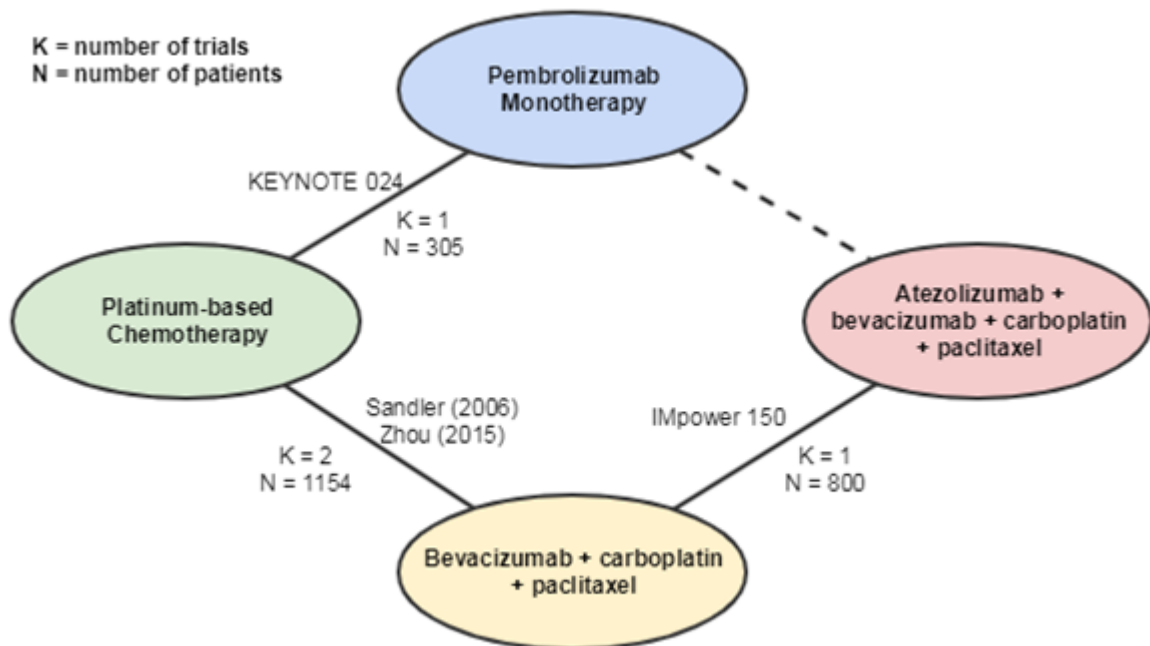
- 6.2 The PBAC noted and welcomed the input from individuals (44), health care professionals (6) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of perceived benefits of treatment with atezolizumab + bevacizumab with PDC, included providing treatment options for those who are PDL-1 negative and those post-progression on TKI therapies, providing a range of treatment choices, overall survival benefits, hope, a perceived understanding of reduced side effects and increased quality of life (QoL) compared to other treatment options, and extension of life. A majority of input was from patients on TKI therapy, or their carers, who were concerned about treatment options when their current therapies stopped working. Affordability of the treatment if it wasn't listed on the PBS was also identified as an issue.
- 6.3 The PBAC noted the advice received from Lung Foundation Australia that the use of atezolizumab + bevacizumab + PDC may extend the time that people with lung cancer have with loved ones and allow them to reach additional milestones, and that the side effects of this combination therapy can be managed.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for atezolizumab + bevacizumab + PDC for the EGFR/ALK wild type subgroup, referring to this population as a high priority and expressing its support for the EGFR/ALK mutation positive sub-group in the submission. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS), which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)* for the EGFR/ALK wild type subgroup and this could not be scored for the EGFR/ALK mutation positive sub group due to the exploratory nature of the analysis of this subgroup in the trial. This support and the ESMO-MCBS scores were both based on the clinical evidence provided by the IMpower150 trial and the comparison with bevacizumab + PDC in that trial.

Clinical trials

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

- 6.5 Two indirect comparisons were presented.
- 6.6 The submission presented an indirect comparison of atezolizumab+ bevacizumab + CP and CP alone, with bevacizumab + CP as the common reference, based on three randomised controlled trials (RCTs):
- IMpower150: a three-armed, open-label, RCT comparing atezolizumab + bevacizumab + CP (N=400) and atezolizumab + CP (N=402) with bevacizumab + CP (N=400) in chemotherapy-naïve patients with Stage IV NSQ NSCLC;
 - Sandler 2006: an open-label RCT comparing bevacizumab + CP (n=417) with CP alone (n=433) in chemotherapy-naïve patients with advanced (Stage IIIB or IV) or recurrent NSQ NSCLC; and
 - Zhou 2015: a randomised, double-blind, placebo-controlled trial comparing first-line bevacizumab + CP (n=138) with placebo + CP (n=138) in Chinese patients with locally advanced, metastatic or recurrent NSQ NSCLC.
- 6.7 The submission also presented a two-step indirect comparison of atezolizumab + bevacizumab + CP with pembrolizumab monotherapy (Figure 1) for patients with EGFR wild type/ALK negative NSQ NSCLC with high PD-L1 expression. A subgroup analysis of patients with EGFR wild type/ALK negative NSQ NSCLC with high PD-L1 expression in IMpower150 (N=136) was used, along with the full analysis sets from Sandler 2006 and Zhou 2015 (unselected by EGFR/ALK mutation status and PD-L1 expression), and Keynote-024. Keynote-024 was an open-label RCT comparing pembrolizumab monotherapy (N=154) with PDC (N=151) in patients with previously untreated advanced NSCLC with PD-L1 tumour proportion score (TPS) $\geq 50\%$ and no sensitising mutation of the EGFR gene or ALK gene translocation.

Figure 1: Network diagram for the indirect comparison of atezolizumab + bevacizumab + CP with pembrolizumab monotherapy presented in the submission.



Note: Only 136/800 of the patients in the relevant treatment arms in IMpower150 were included in this analysis (ITT-WT population with PD-L1 expression TC3 or IC3).

Source: Figure 2.3, p10 'Tecentriq + Avastin PBAC Section 2_Appendix' Attachment 2 to the submission.

6.8 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
IMpower150	Primary CSR: A phase III, open-label, randomized study of MPDL3280A (anti-PDL-1 antibody) in combination with CP with or without Bevacizumab compared with CP + bevacizumab in chemotherapy-pemetrexed patients with stage IV non-squamous non-small cell lung cancer.	January 2018
	Update CSR Study GO29436, (IMpower150) Report No. 1085182	May 2018
	Socinski MA, Jotte RM, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC.	New England Journal of Medicine 2018; 378(24): 2288-2301.
Zhou 2015	Zhou C, Wu YL, Chen G, et al. BEYOND: a randomized double-blind, placebo-controlled, multicentre, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer.	Journal of Clinical Oncology 2015; 33(19): 2197-204.
Sandler 2006	Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.	New England Journal of Medicine 2006; 355(24): 2542-50.
	Sandler A, Yi J, Dahlberg S, et al. Treatment outcomes by tumour histology in Eastern Cooperative Group Study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer.	Journal of Thoracic Oncology 2010; 5(9): 1416-23.
	Dahlberg SE, Sandler AB, Brahmer JR, et al. Clinical course of advanced non-small-cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel in ECOG 4599.	Journal of Clinical Oncology 2010; 28(6): 949-954.
Keynote-024	Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer.	New England Journal of Medicine 2016; 375(19): 1823-33.

CSR = clinical study report; CP = carboplatin + paclitaxel; NSCLC = non-small cell lung cancer.

Source: Table 2.2.1, p81, Table 2.2.2, p82-83 of the submission; Table 2.2, p9 'Tecentriq + Avastin PBAC Section 2_Appendix' Attachment 2 to the submission.

- 6.9 The literature search for trials that would allow an indirect comparison of atezolizumab + bevacizumab + CP with PDC was restricted to identifying trials specifically comparing bevacizumab + CP with CP alone.
- 6.10 The submission did not include four RCTs comparing bevacizumab + PDC versus PDC (Table 3). These were included in the evaluation. The PSCR stated that the entire range of possible trials were not incorporated into a complex set of comparisons, instead CP was used as a proxy for all PDC combinations, simplifying the evidence base for decision making. The PSCR also noted that the results of the expanded indirect treatment comparison (ITC) were not materially different to the comparison presented in the submission. The ESC considered the literature search strategy should have identified all trials of bevacizumab + PDC versus PDC and the submission should have used all these trials in the ITC.

Table 3: Additional trials presented

Trial ID	Protocol title/ Publication title	Publication citation	Reason for exclusion from submission*
Niho 2012	Niho S, Kunitoh H, Nokihara H, et al. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer.	Lung Cancer 2012; 76(3): 362-367.	Results not reported/ other: phase II.**
Zinner 2015	Zinner RG, Obasaju CK, Spigel DR, et al. PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + be followed by maintenance bevacizumab in patients with advanced nonsquamous non-small-cell lung cancer.	Journal of thoracic Oncology 2015; 10(1); 134-142.	Incorrect comparator.: no carboplatin + paclitaxel arm
Galetta 2015	Galetta D, Cinieri S, Pisconti S, et al. Cisplatin/pemetrexed followed by maintenance pemetrexed versus carboplatin/paclitaxel/bevacizumab in advanced nonsquamous lung cancer: the GOIM (Gruppo Oncologico Italia Meridionale) ERACLE phase III randomized trial.	Clinical Lung Cancer 2015; 16(4): 262-273.	Incorrect comparator.: no carboplatin + paclitaxel arm
Reck 2009	Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL).	Journal of Clinical Oncology 2009; 27(8); 1227-1234. Annals of Oncology 2010; 21(9): 1804-1809.	Incorrect intervention: no carboplatin + paclitaxel + bevacizumab arm.

* Source: Excel workbook '2.Avastin + CarboPac Literature Review', 2.Randomised trials, Attachment 1 to the submission.

** This trial could have been excluded on the basis that it only enrolled Japanese patients. However, Zhou 2015, which was included in the submission, only enrolled Chinese patients.

Source: Compiled during the evaluation, based on results of an independent literature search.

6.11 A search of ClinicalTrials.gov, conducted during the evaluation, also located two RCTs comparing atezolizumab + PDC with PDC alone in chemotherapy naïve patients with Stage IV NSQ NSCLC, which would have allowed an indirect comparison of atezolizumab + bevacizumab + CP vs PDC, with atezolizumab + PDC as the common reference. Preliminary results have been published:

- IMpower132: atezolizumab + carboplatin or cisplatin + pemetrexed versus carboplatin or cisplatin + pemetrexed (estimated study completion date November 2019); and
- IMpower130: atezolizumab + carboplatin + nanoparticle albumin-bound (nab) paclitaxel versus carboplatin + nab-paclitaxel (estimated study completion date December 2019).

6.12 The key features of the direct randomised trials are summarised in the table below.

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Atezolizumab + bevacizumab + CP versus bevacizumab + CP						
IMpower150	ITT: 800 ^a ITT-WT ^b : 696	R, OL Median 19.6mths	ITT: OS low, PFS unclear ITT-WT ^c : OS and PFS: high ^b	Stage IV NSQ NSCLC No prior treatment for metastatic disease	OS, PFS	Used
Bevacizumab + PDC versus PDC (1 step indirect comparison)						
Sandler 2006	878	R, OL Median 19 mths	OS: low PFS: unclear	Newly diagnosed Stage IIIB, Stage IV or chemotherapy naïve recurrent NSQ NSCLC	OS, PFS	Used
Zhou 2015	276	R, DB Median 26.9-28.1 mths across arms	OS: low PFS: unclear ^d	Stage IIIB, Stage IV or recurrent NSQ NSCLC Chinese population	OS, PFS	Used
Niho 2012	180	R, OL Median duration not reported	OS: low PFS: unclear	Stage IIIB, Stage IV or recurrent NSQ NSCLC Chemotherapy naïve Japanese population	OS, PFS	Not used
Zinner 2015	361	R, OL Median duration not reported	OS and PFS: high	Stage IV NSQ NSCLC Chemotherapy naïve	OS, PFS	Not used
Galetta 2015	118	R, OL Median 27.0 mths	OS: low PFS: unclear	Stage IIIB or Stage IV NSQ NSCLC Chemotherapy naïve	OS, PFS	Not used
Reck 2009	698	R, DB ^e Median 12.5-12.9 mths across arms	OS: low PFS: unclear	Untreated (first-line) Stage IIIB, Stage IV or recurrent NSQ NSCLC	OS, PFS	Not used
Pembrolizumab versus PDC (2 step indirect comparison)						
Keynote-024	305	R, OL Median 11.2 mths	OS: low PFS: unclear	Untreated (first-line) NSQ or squamous NSCLC, EGFR and ALK negative and TPS ≥50%	OS, PFS	Not used

ALK = anaplastic lymphoma kinase; CP = carboplatin/paclitaxel; DB = double blind; EGFR = epidermal growth factor receptor; ITT = intention to treat; ITT-WT = intention to treat wild type; NSCLC = non-small cell lung cancer; NSQ = non-squamous; OL = open label; OS = overall survival; PDC = platinum doublet chemotherapy; PFS=progression-free survival; R=randomised; TPS = tumour proportion score.

^a ITT population in the atezolizumab + bevacizumab + CP and the bevacizumab + CP arms. An additional 402 patients were included in the atezolizumab + CP arm.

^b A protocol amendment in version 6 of the protocol (March 2017) changed the primary analysis population from the ITT population to the ITT-WT population, which excluded patients in both arms with known sensitising EGFR mutation or ALK translocations and potentially introduced imbalances between treatment arms in unmeasured confounders.

^c The ITT-WT analysis population was used in the 2-step indirect comparison of atezolizumab + bevacizumab + CP versus pembrolizumab monotherapy.

^d PFS was calculated after censoring for non-protocol therapy. The extent of censoring was not reported.

^e While Reck 2009 was double-blind, in the original protocol, patients who completed six cycles of PDC had the option to of unblinding and patients assigned to bevacizumab were permitted to continue with single-agent bevacizumab. A protocol amendment eliminated the optional unblinding but the proportion of patients whose treatment assignment was unblinded during the treatment phase was not reported.

Source: Compiled during the evaluation, based on Table 2.3.2, pp91-93, Table 2.3.3, p95 and Table 2.3.4, p97 of the submission; Niho 2012, Zinner 2015; Galetta 2015; Reck 2009; Reck 2016.

6.13 Given the open-label design of the majority of the trials, the evaluation considered there was potential for both performance and detection bias, especially for outcomes

with some degree of subjectivity. However, with the exception of Zinner 2015 and the intention to treat wild type population (ITT-WT) analysis in IMpower150[†], the risk of bias was relatively low for the most patient-relevant outcome of overall survival (OS) in each trial.

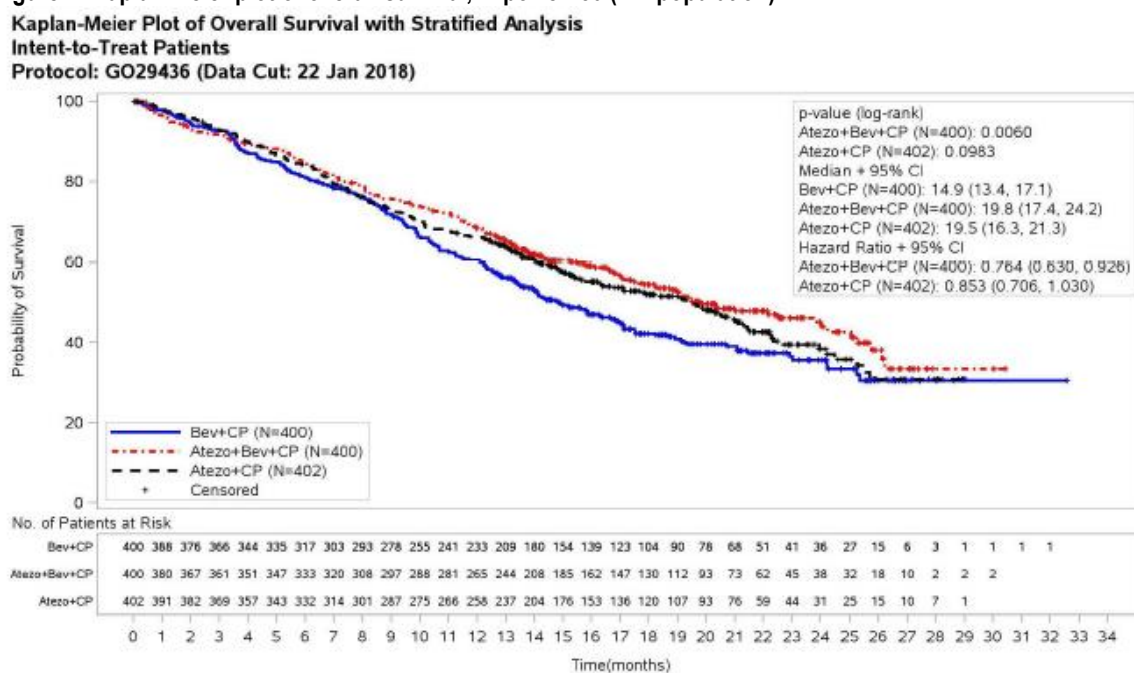
- 6.14 None of the patients in the trials comparing bevacizumab + PDC with PDC received immunotherapy following progression. In addition, only Zinner 2015 and Galetta 2015 allowed maintenance therapy with pemetrexed following completion of PDC.

Comparative effectiveness

Direct comparison: atezolizumab + bevacizumab + CP vs bevacizumab + CP

- 6.15 The Kaplan-Meier curves of OS and progression free survival (PFS) for the intention to treat (ITT) population in IMpower150 are presented in Figure 2 and Figure 3, respectively.

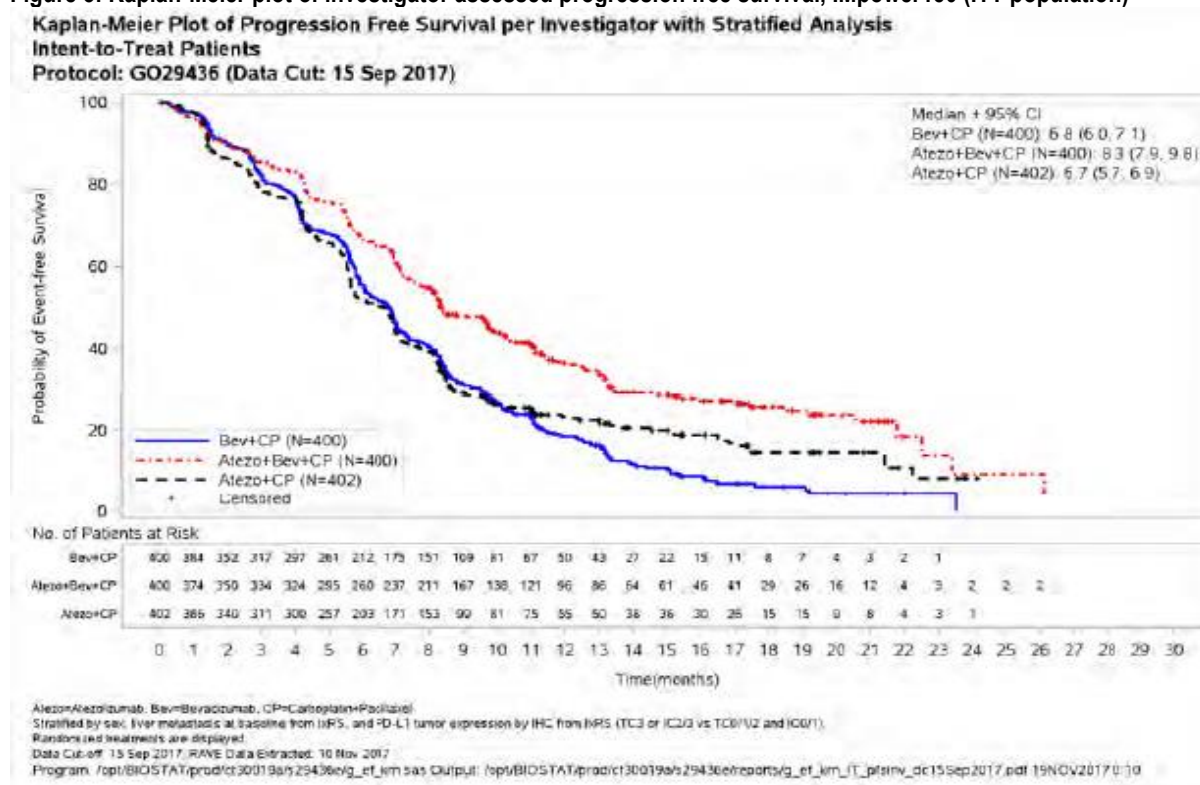
Figure 2: Kaplan-Meier plot of overall survival, IMpower150 (ITT population)



Atezo = atezolizumab; Bev = bevacizumab; CI = confidence interval; CP = carboplatin + paclitaxel; ITT = intention to treat
Source: Figure 8, p85 of the IMpower150 Updated CSR (May 2018).

[†] The ITT-WT population in IMpower150 excluded patients with known sensitising EGFR mutations or ALK translocations; randomisation was not stratified by EGFR/ALK mutation status. There was considerable risk of attrition bias in Zinner 2015.

Figure 3: Kaplan-Meier plot of investigator assessed progression free survival, IMpower150 (ITT population)



Atezo = atezolizumab; Bev = bevacizumab; CI = confidence interval; CP = carboplatin + paclitaxel; ITT = intention to treat
 Source: Figure 10, p147 IMpower150 CSR (January 2018)

- 6.16 There was a statistically significant improvement in both OS and PFS with atezolizumab + bevacizumab + CP compared with bevacizumab + CP in the ITT population. The observed improvement in OS met the American Society of Clinical Oncology lung cancer working group’s recommended targets for meaningful clinical trial goals for NSQ NSCLC[‡]. The ESC noted that there was negligible difference in median OS between atezolizumab + bevacizumab + CP (19.8 months) versus atezolizumab + CP (19.5 months).
- 6.17 The evaluation and ESC noted that there was minimal difference in the OS rate between the three treatment arms over the first 8 months of treatment, with separation of the survival curves evident beyond this time point. The ESC considered that this suggested the proportional hazards assumption may not be valid and, therefore, the estimated hazard ratio (HR) should be interpreted with caution.
- 6.18 In IMpower150, health related quality of life and treatment burden/tolerability were assessed using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core (C30) and lung cancer (LC13)

[‡] Improvement in median OS of 3.25-4 months over current median OS, with an associated hazard ratio of 0.76-0.8. Ellis LM, Bernstein DS, *et al.* American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol.* 2014; 32 (12):1277-80.

modules. Completion rates were high (>80%) for both the EORTC QLQ-C30 and LC13 across treatment arms throughout the course of treatment. The submission stated that the EuroQol five dimensions 3-level (EQ-5D-3L) questionnaire was also completed. The EQ-5D scores from IMpower150 were used to derive the utility values for the health states in the modelled economic evaluation.

- 6.19 The submission stated that the change in scores over time suggested that the EORTC QLQ-C30 global health status and physical function mean scores in each arm returned to baseline scores following the completion of chemotherapy and numerically improved thereafter. It also claimed that patients in all arms, on average, did not report clinically meaningful worsening at any point on treatment for multiple treatment-related symptoms, including fatigue, constipation, diarrhoea, nausea/vomiting, haemoptysis, dysphagia, and sore mouth. A clinically meaningful worsening was initially observed in both patient-reported neuropathy and alopecia in all treatment arms. This attenuated over time. As the questionnaires were completed prior to administration of study drug, the evaluation considered it is likely that they failed to capture the full impact of drug-related adverse events (AEs) on QoL. The PSCR disagreed that drug-related outcomes were not fully captured and quoted FDA guidance recommending that patient reported outcome measures be administered before other assessments or procedures. The ESC considered that the timing of conduct of the EORTC QLQ-C30, prior to administration of treatment and reflecting back upon only one week prior to the conduct of the questionnaire, missed the first two weeks post administration of each treatment dose of the three week administration schedule, which was a gap in the reporting of outcomes, particularly those evident soon after administration. The ESC considered that QoL data collected in IMpower150 would not capture the full impact of drug-related AEs of adding atezolizumab and bevacizumab to PDC.

Indirect treatment comparison: atezolizumab + bevacizumab + PDC vs PDC

- 6.20 The results for the indirect comparison of atezolizumab + bevacizumab + CP vs CP, based on the results from IMpower150, Sandler 2006 and Zhou 2015, as presented in the submission, as well as the additional analyses performed during the evaluation, are presented in Table 5.

Table 5: OS and PFS results for the indirect comparison of atezolizumab + bevacizumab + CP vs PDC

Analysis population	ATEZO + BEV + CP vs bevacizumab + CP	PDC vs bevacizumab + PDC	Indirect HR (95% CI)	p-value
Overall survival				
Submission analysis ^a	0.76 (0.63, 0.93)	1.31 (1.13, 1.50) ^a	0.58 (0.46, 0.74)	0.000
All 6 BEV + PDC vs PDC trials ^b	0.76 (0.63, 0.93)	1.10 (0.96, 1.25) ^b	0.69 (0.54, 0.87)	0.002
Excluding Asian trials ^c	0.76 (0.63, 0.93)	1.08 (0.92, 1.23) ^c	0.71 (0.55, 0.90)	0.005
Progression free survival				
Submission analysis ^a	0.59 (0.50, 0.69)	1.91 (1.17, 3.11) ^a	0.31 (0.18, 0.51)	0.000
All 6 BEV + PDC vs PDC trials ^b	0.59 (0.50, 0.69)	1.32 (1.02, 1.62) ^b	0.44 (0.34, 0.59)	0.000
Excluding Asian trials ^c	0.59 (0.50, 0.69)	1.15 (0.88, 1.42) ^c	0.51 (0.38, 0.68)	0.000

ATEZO = atezolizumab; BEV = bevacizumab; CI = confidence interval; CP = carboplatin/paclitaxel; HR = hazard ratio; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression free survival.

^a PDC vs bevacizumab + CP HR from meta-analysis of Sandler 2006 and Zhou 2015

^b PDC vs bevacizumab + CP HR from meta-analyses of Sandler 2006, Zhou 2015, Niho 2012, Zinner 2015, Galetta 2015 and Reck 2009.

^c PDC vs bevacizumab + CP HR from meta-analyses of Sandler 2006, Zinner 2015, Galetta 2015 and Reck 2009.

Statistically significant results are presented in bold type

Figures in italics were calculated during the evaluation.

Source: Table 2.6.3 p162 and Table 2.6.4 p163 of the submission; Excel workbook 'ITC', Folder 'Section 2 Spreadsheets' supplied with the submission. Figures in italics were calculated during the evaluation using the 'ITC' Excel workbook supplied in the evaluation.

- 6.21 The ESC considered were a number of transitivity issues across the trials including the duration of follow up, baseline populations, time period over which the trials were conducted, subsequent therapies and treatment protocols.
- 6.22 In IMpower150, 35.5% of all patients in the common reference arm (bevacizumab + CP) of IMpower150 received immunotherapy while none of the patients in either arm of the comparator trials received immunotherapy at any subsequent line of therapy. The ESC considered it was not possible to predict either the magnitude or the direction of any effect on the observed HR for OS for bevacizumab + PDC versus PDC resulting from patients in both treatment arms not receiving later line immunotherapy, and, consequently, on the results of the indirect comparison of OS.
- 6.23 The ESC considered the ITC supported an efficacy benefit in OS and PFS for treatment with atezolizumab + bevacizumab + PDC versus PDC. However, the magnitude of the benefit was uncertain given the significant transitivity issues identified.

Indirect treatment comparison: atezolizumab + bevacizumab + PDC vs pembrolizumab

- 6.24 The results of the 2-step indirect comparison of atezolizumab + bevacizumab + CP with pembrolizumab monotherapy in patients with EGFR wild type/ALK positive, high PD-L1 expression NSCLC are presented in Table 6.

Table 6: Results for the 2-step indirect comparison of atezolizumab + bevacizumab+ CP vs pembrolizumab monotherapy in patients with EGFR wild type/ALK negative high PD-L1 expression NSCLC

Step 1: Indirect comparison of atezolizumab + bevacizumab + CP in the PD-L1 high WT population (IMpower150) with CP in the ITT/FAS population unselected by PD-L1 status (Sandler 2006 and Zhou 2015)				
	ATEZO + BEV + CP vs bevacizumab + CP	CP vs bevacizumab + CP	Indirect HR (95% CI)	p-value
OS	0.70 (0.43, 1.13)	1.31 (1.13, 1.50) ^a	0.53 (0.32, 0.88)	0.015
PFS	0.34 (0.22, 0.52)	1.91 (1.17, 3.11) ^a	0.18 (0.09, 0.34)	0.000
Step 2: Indirect comparison of results from Step 1 with the ITT population and the NSQ subgroup in Keynote-024				
	ATEZO + BEV + CP vs CP (from step 1)	Keynote-024 pembrolizumab vs PDC	Indirect HR (95% CI)	p-value
OS				
Keynote-024 ITT	0.53 (0.32, 0.88)	0.60 (0.41, 0.89)	0.89 (0.48, 1.65)	0.714
PFS				
Keynote-024 ITT	0.18 (0.09, 0.34)	0.50 (0.37, 0.68)	0.36 (0.21, 0.60)	0.000
Keynote-024 NSQ subgroup	0.18 (0.09, 0.34)	0.55 (0.39, 0.76)	0.32 (0.23, 0.45)	0.000

ALK = anaplastic lymphoma kinase; ATEZO = atezolizumab; BEV = bevacizumab; CI = confidence interval; CP = carboplatin/paclitaxel; EGFR = epidermal growth factor receptor; FAS = full analysis set; HR = hazard ratio; ITT = intention to treat; PD-L1 = programmed cell death ligand 1; NSQ = non-squamous; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression free survival; WT = wild type

Source: Table 2.14, p32, Table 2.16, p33, Table 2.25, p41 and Table 2.26, p 42 Attachment 2 to the submission; Spreadsheets 'Pembro Keynote-024', 'ITC 1 ABCP vs CP' and 'ITC 2 ABCP vs Pembro' Excel workbook 'ITC', Section 2 spreadsheets, supplied with the submission.

6.25 In each step of the indirect comparison, the patient populations in the common reference arm differed in terms of both EGFR/ALK mutation status and PD-L1 expression status. In addition to the transitivity issues outlined above for the indirect comparison of atezolizumab + bevacizumab + CP with PDC, this comparison relied on a subgroup analysis from IMpower150, and the OS results from Keynote-024 were only reported for the ITT population, in which approximately 18% of patients had predominantly squamous NSCLC.

Comparative harms

6.26 The key adverse events in IMpower150 are summarised in Table 7.

Table 7: Summary of key adverse events in IMpower150 (safety population)

	ATEZO+BEV+CP N=393 n (%)	ATEZO+CP arm N=400 n (%)	BEV+CP arm N=394 n (%)
Median duration of treatment, months			
Atezolizumab	8.3 months	6.4 months	-
Bevacizumab	6.7 months	-	5.1 months
Total number of patients with at least one AE	386 (98.2%)	391 (97.8%)	390 (99.0%)
Total number of events	6419	4851	4630
Total number of patients with at least one:			
Treatment-related AE	370 (94.1%)	377 (94.3%)	377 (95.7%)
Deaths due to AE (Grade 5 AE)	24 (6.1%) ^a	10 (2.5%)	21 (5.3%) ^b
Treatment-related Grade 5 AE	11 (2.8%)	4 (1.0%)	9 (2.3%)
Related to atezolizumab treatment	1	3	-
Related to bevacizumab treatment	4	-	8
Related to both atezolizumab and bevacizumab	4	-	-
AE leading to withdrawal from any treatment	133 (33.8%) ^{c, d}	53 (13.3%)	98 (24.9%) ^e
AE leading to any dose modification/ interruption	246 (62.6%)	207 (51.8%)	188 (47.7%)
Serious Adverse Event	174 (44.3%)	157 (39.3%)	135 (34.3%)
Treatment-Related Serious Adverse Event	103 (26.2%) ^f	78 (19.5%)	78 (19.8%)
Grade 3-4 AE	250 (63.6%)	230 (57.5%)	230 (58.4%)
Treatment-related Grade 3-4 AE	223 (56.7%) ^g	172 (43.0%)	191 (48.5%)

AE = adverse event; ATEZO = atezolizumab; BEV = bevacizumab; CP = carboplatin/paclitaxel

^a Relative risk (RR) of death due to AE vs atezolizumab + CP: 2.4 (95% CI: 1.2, 5.0)

^b RR of death due to AE vs atezolizumab + CP: 2.1 (95% CI: 1.0, 4.5)

^c RR of AE leading to withdrawal vs bevacizumab + CP: 1.4 (95% CI: 1.1, 1.7)

^d RR of AE leading to withdrawal vs atezolizumab + CP: 2.6 (95% CI: 1.9, 3.4)

^e RR of AE leading to withdrawal vs atezolizumab + CP: 1.9 (95% CI: 1.4, 2.5)

^f RR treatment related severe AE, vs bevacizumab + CP: 1.3 (95% CI: 1.0, 1.7), vs atezolizumab + CP: 1.3 (95% CI: 1.0, 1.7)

^g RR treatment related Grad 3-4 AE, vs bevacizumab + CP: 1.2 (95% CI: 1.0, 1.3), vs atezolizumab + CP: 1.3 (95% CI: 1.1, 1.5)

Relative risks were calculated during the evaluation.

* January 2018 data cut (IMpower150 CSR Update, May 2018)

Source: Table 2.5.14, p139 of the submission.

6.27 The safety data indicated that both atezolizumab + bevacizumab + CP and bevacizumab + CP were associated with significantly more deaths due to AEs and AEs leading to withdrawal from treatment compared with atezolizumab + CP. The addition of atezolizumab to bevacizumab + CP was associated with significantly higher incidence of AEs leading to treatment discontinuation, treatment related serious AEs and treatment-related Grade 3-4 AEs.

6.28 The submission did not perform an indirect comparison of safety due to the limited data reported in both Sandler 2006 and Zhou 2015. In addition, comparison of safety event rates across the trials were confounded by the difference in duration of follow-up and extent of exposure to study drugs. Due to this, the magnitude of the increase in harms associated with the addition of atezolizumab and bevacizumab to PDC could not be reliably determined.

Benefits/harms

6.29 Based on the results of IMpower150, atezolizumab + bevacizumab + CP was found to result in a median increase in progression free survival of approximately 1.6 months

compared to bevacizumab + CP and a median increase in overall survival of 4.9 months compared to bevacizumab + CP.

Clinical claim

- 6.30 The submission described atezolizumab + bevacizumab + PDC as superior in terms of effectiveness and inferior in terms of safety compared with PDC alone for both EGFR wild type/ALK negative patients, and for EGFR mutant/ALK positive patients after TKI therapy. The submission claimed that the safety profile of atezolizumab + bevacizumab + PDC remained acceptable and manageable.
- 6.31 The submission described atezolizumab + bevacizumab + PDC as non-inferior in terms of effectiveness and inferior in terms of safety compared with pembrolizumab monotherapy in patients with EGFR wild type/ALK negative NSQ NSCLC with high PD-L1 expression.
- 6.32 The PBAC considered that the claim of superior comparative effectiveness to PDC in EGFR wild type/ALK negative patients was reasonable, however the incremental benefit of the inclusion of bevacizumab was uncertain.
- 6.33 The PBAC considered that the claim of inferior comparative safety to PDC in EGFR wild type/ALK negative patients was reasonable, and that the toxicities were known and likely manageable in practice.
- 6.34 The PBAC considered that the claim of superior comparative effectiveness to PDC in EGFR mutant/ALK positive patients after TKI therapy was reasonable, but noted that this was based on an ITC of a small subgroup and so the magnitude of the benefit remained highly uncertain.
- 6.35 The PBAC considered that the claim of inferior comparative safety to PDC in EGFR mutant/ALK positive patients after TKI therapy was reasonable, and that the toxicities were known and likely manageable in practice.
- 6.36 The PBAC considered the claim that atezolizumab + bevacizumab + PDC has non-inferior effectiveness and inferior safety compared with pembrolizumab monotherapy in patients with EGFR wild type/ALK negative NSQ NSCLC with high PD-L1 expression to be uncertain but reasonable, and that the toxicities were known and likely manageable in practice.

Economic analysis

Cost effectiveness analysis

- 6.37 The submission presented a modelled economic evaluation based on the indirect comparison of randomised trials, which has been presented above. The type of economic evaluation was a cost-utility analysis. The key components of the economic evaluation are summarised below.

Table 8: Summary of model structure and rationale

Component	Description
Type of analysis	Cost-utility analysis (CUA)
Outcomes	Life-years (LY) gained and quality-adjusted life-years (QALY) gained
Time horizon	7.5 years in the model base case vs ~20 months median follow-up in the IMpower150 trial
Method/s used to generate results	Partitioned survival cohort analysis
Health states	Three: progression-free disease, progressed disease and death
Cycle length	1 week
Transition probabilities	Health state allocation over time in the atezolizumab + bevacizumab + PDC arm was determined by PFS and OS curves from IMpower150 at 22 January 2018 clinical cut-off until the median duration of follow-up of 20 months. Beyond 20 months, parametric extrapolations of both PFS and OS curves were applied. PDC outcomes were estimated by adjusting the survival curves of bevacizumab + CP observed from IMpower150 with the hazard ratios estimated from the comparator trials (Sandler 2006 and Zhou 2015) for bevacizumab+ CP vs CP until 20 months and extrapolated using parametric functions beyond then.
Software	Microsoft Excel

PDC = platinum doublet chemotherapy; PFS = progression-free survival; OS = overall survival; CP = carboplatin and paclitaxel.
Source: Table 3.1.1, p184 of the submission.

6.38 The submission presented a stepped economic evaluation. During the evaluation, it was noted that the costs of subsequent therapies post-progression had been included from Step 1 in the submission’s stepped analysis, and the proposed effective prices for atezolizumab and bevacizumab were applied only to the last step. In order to enable a clear demonstration of the impact of each key modelling step during the evaluation, costs of subsequent therapies post-progression were removed until Step 5. In addition, effective prices for atezolizumab and bevacizumab were applied from Step 1. The revised stepped economic evaluation is presented below.

Table 9: Revised steps during the evaluation for the economic modelling

Step	Costs	Outcomes
Step 1 trial-based, 20 months of median trial follow-up, incorporation of trial-based utility values to determine QALYs	Medicine costs	LYG QALYs
Step 2 modelled evaluation across 7.5 year time horizon, extrapolation from the trial median follow-up	As in Step 1	As in Step 1
Step 3 incorporation of administration and MRU costs	As in Step 1 + costs of administration and MRU	As in Step 1
Step 4 incorporation of AE related costs	As in Step 3 + costs of AEs	As in Step 1
Step 5 inclusion of the costs of subsequent therapies post-progression	As in Step 4 + cost of subsequent therapies	As in Step 1
Step 6 inclusion of end of life costs	As in Step 5 + end of life costs	As in Step 1

LYG = life year gained; QALY = quality adjusted life year; MRU = medical resource use; AE = adverse event.
Effective prices for atezolizumab and bevacizumab have been applied throughout the steps of the model.
Source: Compiled during the evaluation based on Table 3.1.2, p186 of the submission.

- 6.39 The submission presented the modelled economic evaluation for three populations:
- the EGFR wild type/ALK negative (ITT-WT) population; and
 - the EGFR mutant/ALK positive population; and
 - the ITT population which incorporated both populations above and reflected the ITT population in IMpower150.
- 6.40 The ESC considered that the results of the subgroup analyses should be treated as exploratory, given the low number of patients in the EGFR mutant/ALK positive subgroup (13%) in IMpower150 and in both subgroups in Zhou 2015, and the fact that randomisation was not stratified by tumour mutation status in either trial. These issues are in addition to the uncertainties introduced by the indirect comparison for the ITT population using trials with substantial transitivity concerns. The PSCR stated that the subgroup was pre-specified in the analysis plan and stated that IMpower150 is the only immunotherapy trial to have demonstrated a benefit for the post TKI treatment population.
- 6.41 The submission acknowledged that standard of care in Australia for chemotherapy naïve Stage IV NSQ NSCLC was PDC, which was not a treatment option for patients in the IMpower150 trial. Therefore, the treatment effect of PDC relied on data from Sandler 2006 and Zhou 2015. The HRs of bevacizumab + CP vs CP observed from these two trials were applied to the survival curves of bevacizumab + CP in IMpower150 to estimate the survival curves of PDC in the model. The evaluation noted there were substantial transitivity concerns among the trials in the indirect comparison.
- 6.42 In addition, as noted above, other potentially relevant comparator trials were excluded from the submission. The HRs for bevacizumab + PDC versus PDC obtained from the meta-analysis of all the relevant comparator trials were examined in sensitivity analyses during the evaluation.
- 6.43 The submission extrapolated the PFS and OS curves for both the atezolizumab + bevacizumab + PDC arm and the PDC arm from the median duration of follow-up (20 months) in IMpower150 to 7.5 years in the base case. A Weibull function was used to extrapolate PFS and an exponential function was used to extrapolate OS in both treatment arms. The ESC noted the model was sensitive to the function used to extrapolate OS but considered the use of an exponential function was reasonable.
- 6.44 For both the extrapolations of PFS and OS, a continued treatment effect was implicitly assumed by applying the chosen parametric functions beyond trial duration until the end of the modelled time horizon. The OS curve for the atezolizumab + bevacizumab + PDC arm did not converge with the OS curve for the PDC arm within the base case time horizon of 7.5 years. When considering pembrolizumab for the first-line treatment of patients with metastatic (Stage IV) NSCLC, the PBAC advised that “the base case of the economic model would need to converge the extrapolation curves to the base case time horizon of 7.5 years” (paragraph 7.13, Item 7.07, Pembrolizumab

Public Summary Document (PSD), November 2017 PBAC meeting). The ESC recalled the curves for the pembrolizumab model converged from 5 years⁵.

- 6.45 In IMpower150, atezolizumab was administered until loss of clinical benefit whereas bevacizumab was until progression. Therefore, time to treatment discontinuation (TTD) was analysed separately for each individual treatment within the intervention arm. The submission considered an exponential function to be the best fit to TTD of the intervention arm in all modelled populations for both atezolizumab and bevacizumab. The ESC considered the exponential function appeared to provide the best fit to the within-trial TTD data among all the distribution functions provided in the submission.
- 6.46 The evaluation noted that disutility associated with the AEs from atezolizumab and bevacizumab additional to those from PDC was not considered in the submission and, given the harms associated with the atezolizumab + bevacizumab + PDC over PDC alone, had the potential to bias the result to favour the intervention arm. The additional intravenous infusions with the atezolizumab + bevacizumab + PDC may also have adversely impacted the patients' QoL. The cost to manage AEs in the intervention arm was included in the submission's model. The PSCR stated that no disutilities were applied in the model and rather these were assumed to have been captured within the utility weights used in the economic evaluation. The PSCR stated an "extreme disutility" approach was explored and had a marginal impact on the incremental cost effectiveness ratio (ICER). The ESC noted that mean utilities were calculated for the PFS and Progression health states using pooled utility scores from patients in the atezolizumab + bevacizumab + CP arm and bevacizumab + CP arms in the ITT population of IMpower150. The ESC considered the model structure did not account for the disutility of adding atezolizumab and bevacizumab to PDC as utilities were applied according to health state. Further, the ESC considered the reduction in QoL associated with treatment may not have been captured in the clinical trial due to how and when the data were collected (see paragraph 6.19).
- 6.47 The key drivers of the model are summarised below.

⁵ paragraph 5.6, Item 4.07, Pembrolizumab PSD, March 2018 PBAC meeting

Table 10: Key drivers of the model

Description	Method/Value	Impact
Treatment effect of atezolizumab + bevacizumab + PDC versus PDC	OS curve for the PDC arm was derived by adjusting the OS curve of the bevacizumab + CP arm in IMpower150 with the HR observed from Sandler 2006 and Zhou 2015	High, favours atezolizumab + bevacizumab + PDC
Extrapolation	Exponential distributions for OS extrapolation for both of the IMpower150 trial arms were applied in the base case.	Moderate – High, favours atezolizumab + bevacizumab + PDC
	Assumed continuing treatment effect through application of PFS and OS HRs estimated from bevacizumab + PDC vs. PDC trials.	Moderate - High , favours atezolizumab + bevacizumab + PDC
	OS curves for the two comparative arms did not converge within the base case time horizon of 7.5 years.	High, favours atezolizumab + bevacizumab + PDC
Subsequent CIT post-progression in the comparator arm	Inclusion of the costs of immunotherapy post-progression in █% of the comparator arm (compared to 35% in the IMpower150 trial) with no change in OS.	High, favours atezolizumab + bevacizumab + PDC
Utility	No disutility assumed for the additional AEs or IV infusions in the intervention arm	Uncertain of the size of the impact, favours atezolizumab + bevacizumab + PDC

PDC = platinum doublet chemotherapy; CIT = cancer immunotherapy; AE = adverse event; IV = intravenous.

Source: Compiled based on sensitivity analyses performed during the evaluation.

6.48 The results of the revised stepped analyses for the ITT population are presented below.

Table 11: Results of the revised stepped economic evaluation for the ITT population

Step and component	ATEZO + BEV + PDC	PDC	Increment
Step 1: trial-based costs and outcomes			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	1.205	1.006	0.199
QALYs	0.864	0.715	0.149
Incremental cost/extra LYG gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 2: extension of time horizon to 7.5 years			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	2.175	1.390	0.785
QALYs	1.549	0.984	0.565
Incremental cost/extra LYG gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 3: incorporation of administration and MRU costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	2.175	1.390	0.785
QALYs	1.549	0.984	0.565
Incremental cost/extra LYG gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 4: incorporation of AE costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	2.175	1.390	0.785
QALYs	1.549	0.984	0.565
Incremental cost/extra LYG gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 5: inclusion of the costs of subsequent therapies post progression			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	2.175	1.390	0.785
QALYs	1.549	0.984	0.565
Incremental cost/extra LYG gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 6: inclusion of the end of life costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	2.175	1.390	0.785
QALYs	1.549	0.984	0.565
Incremental cost/extra LYG gained			\$ [REDACTED]
Incremental cost/extra QALY gained (base case)			\$ [REDACTED]

ATEZO = atezolizumab; BEV = bevacizumab; PDC = platinum doublet chemotherapy; MRU = medical resource use; LYG = life year gained; QALY = quality-adjusted life year; AE = adverse event; TTD = time to treatment discontinuation; PFS = progression free survival; OS = overall survival

Source: compiled during the evaluation based on Economic Evaluation.xlsx, worksheet "Result Table" by changing the variable I37 and M37 in the worksheet "Treatment costs" to "=IF(step<1,0,rebate_atezo)" and "=IF(step<1,0,rebate_bev)", and setting the cost of subsequent therapy E51 and H51 in the worksheet "Result Table" to zero from Step 1 to Step 4. .

The redacted table show ICERs in the range of \$15,000/QALY - \$200,000/QALY.

6.49 The results of the revised stepped analyses indicated that two steps had the most impact on the final ICER: extension of time horizon to 7.5 years and inclusion of the costs of subsequent therapies post-progression.

6.50 The key sensitivity analyses presented in the submission and performed during the evaluation for the ITT population are summarised below.

Table 12: Results of key sensitivity analyses for the ITT population

Analyses	Incremental cost	Incremental QALY	ICER (\$/QALY)
Base case	\$ [redacted]	0.565	\$ [redacted]
The proportion of progressed patients in the comparator arm who received subsequent immunotherapy (base case [redacted]%)			
35%*	\$ [redacted]	0.565	\$ [redacted]
80%	\$ [redacted]	0.565	\$ [redacted]
Time horizon (base case 7.5 years)			
3 years	\$ [redacted]	0.317	\$ [redacted]
5 years	\$ [redacted]	0.476	\$ [redacted]
10 years	\$ [redacted]	0.596	\$ [redacted]
Extrapolation for OS for both arms (base case exponential extrapolation)			
Gamma extrapolation	\$ [redacted]	0.391	\$ [redacted]
Gompertz extrapolation	\$ [redacted]	0.423	\$ [redacted]
Weibull extrapolation	\$ [redacted]	0.545	\$ [redacted]
HRs of PFS and OS for BEV + PDC vs PDC (base case 0.52 and 0.77 respectively)			
0.73 for PFS and 0.88 for OS (point estimates using all trials)	\$ [redacted]	0.442	\$ [redacted]

QALY = quality adjusted life year; ICER = incremental cost effectiveness ratio; HR = hazard ratio; PFS = progression free survival; OS = overall survival; BEV = bevacizumab; PDC = platinum doublet chemotherapy; CI = confidence interval.

* Reflects the proportion of patients in bevacizumab + CP arm of IMpower 150 that received immunotherapy

Source: Compiled during the evaluation using data from Economic Evaluation.xlsx

The redacted table show ICERs in the range of \$45,000/QALY - \$105,000/QALY.

- 6.51 The model was sensitive to the treatment effect of atezolizumab + bevacizumab + PDC relative to PDC. The evaluation noted that the application of the meta-analysed HRs for bevacizumab + CP versus CP, from Sandler 2006 and Zhou 2015, to the survival curves of the bevacizumab + CP arm in IMpower150 may not reflect the benefit of PDC, given the substantial transitivity concerns among IMpower150, Sandler 2006 and Zhou 2015. When meta-analysing all the potentially relevant comparator trials to estimate the HRs for bevacizumab + PDC versus PDC, the ICER increased to \$45,000 - \$75,000 per QALY for the ITT population.
- 6.52 The model was also sensitive to the proportion of progressed patients in the comparator arm who received post-progression immunotherapies. When proportions were changed (35% and 80% versus the base case of [redacted]%) in the sensitivity analyses, the ICER ranged from \$15,000/QALY to \$105,000/QALY. The health benefit from the comparator arm did not change with the proportion of patients receiving post-progression immunotherapies. The ESC noted that 35.5% of all patients in the bevacizumab + CP treatment arm received immunotherapy post-progression. The ESC considered the use of [redacted]% was more likely to reflect clinical practice but also noted OS in the model was not adjusted to account for the increased use of immunotherapy.
- 6.53 The ESC considered the base case model should converge OS at 7.5 years, commencing at 5 years to be consistent with the first-line pembrolizumab monotherapy model that was considered acceptable to the PBAC. The ESC noted the ICER applying convergence in this way was \$45,000 - \$75,000 at the submission's proposed price.

6.54 The PBAC noted the sponsor had offered a [REDACTED] % discount on the submission’s proposed price and this reduced the ICER calculated by the ESC to \$45,000 - \$75,000.

Cost minimisation versus pembrolizumab

6.55 A comparison of the cost of a treatment cycle of atezolizumab + bevacizumab versus pembrolizumab is included in Table 13. The cost of PDC is not included as patients who progress on pembrolizumab will likely receive treatment with chemotherapy.

Committee-In-Confidence information

Table 13: Cost per treatment cycle of atezolizumab+bevacizumab versus pembrolizumab

	Pembrolizumab	Pembrolizumab	Atezolizumab + bevacizumab
AEMP per treatment cycle ¹	[REDACTED]	[REDACTED]	\$ [REDACTED] ²
DPMQ per treatment cycle	[REDACTED]	[REDACTED]	[REDACTED]
Public hospital	[REDACTED]	[REDACTED]	\$ [REDACTED] ³
Private hospital	[REDACTED]	[REDACTED]	\$ [REDACTED]
Weighted ⁴	[REDACTED]	[REDACTED]	\$ [REDACTED]

AEMP approved ex-manufacturer price; DPMQ dispensed price for maximum quantity

1. Treatment cycle for pembrolizumab = 200 mg; for atezolizumab = 1,200 mg
2. Assumes AEMP for bevacizumab [REDACTED]
3. Includes mark-ups and dispensing fees of \$ [REDACTED] (public) and \$ [REDACTED] (private) for bevacizumab
4. Assumes public/private weightings as per atezolizumab + bevacizumab submission: 32.6% public, 67.4% private.



End Committee-in-Confidence information

Drug cost/patient/course

6.57 At the price proposed in the submission, the total treatment costs with atezolizumab + bevacizumab + CP were \$ [REDACTED], for a full treatment course, assuming an average patient of 72kg, mean body surface area of 1.82m², and 32.6% treatments being in public setting versus 67.4% in private setting. Atezolizumab and bevacizumab were given for approximately [REDACTED] weeks ([REDACTED] months) and [REDACTED] weeks ([REDACTED] months) respectively, based on the extrapolated TTD curves in the base case model for the ITT population, and CP was given for 6 cycles. Treatment with carboplatin and paclitaxel, under the same assumptions, cost \$1,680. The Pre-PBAC Response stated the cost per treatment course, incorporating the revised price offer in the Pre-PBAC Response was \$ [REDACTED], or \$ [REDACTED] per year.

6.58 The PBAC noted that the assumed duration of a treatment course for atezolizumab was longer than for pembrolizumab in the monotherapy submission. The PBAC noted that patients in IMpower150 received atezolizumab until loss of clinical benefit and bevacizumab until disease progression while in KEYNOTE-024 patients were treated until disease progression. The PBAC considered it unlikely a difference in treatment duration would be observed in clinical practice, particularly as the continuing criteria are similar (patients must have ‘stable or responding disease’, which is a different way

of saying “the patient must not have progressive disease”). The PBAC noted the cost of a course of treatment of atezolizumab + bevacizumab + CP will therefore be reduced from that presented in the pre-PBAC response.

Estimated PBS usage & financial implications

- 6.59 This submission was not considered by DUSC. The submission used a combination of epidemiology and market share approaches to estimate the financial implications associated with the proposed listing of atezolizumab + bevacizumab. The estimation of the eligible population was based on Australian Institute of Health and Welfare lung cancer incidence data, epidemiological data from a retrospective survey of patients from the Victorian Cancer Registry **, PBAC and MSAC PSDs and DUSC reports.
- 6.60 The use of PDC in combination with atezolizumab + bevacizumab was assumed to be offset by the decrease in the use of PDC alone. This was reasonable.
- 6.61 The financial estimates incorporated the expected increase in the use of later-line chemotherapy (PDC and pemetrexed) following progression on atezolizumab + bevacizumab + PDC, and the decrease in post-progression therapies currently used following PDC (immunotherapy and docetaxel). The assumptions used in these estimates were consistent with those in the economic evaluation.
- 6.62 The submission’s estimated financial implications of listing atezolizumab + bevacizumab on the PBS for use in combination with PDC for the treatment of metastatic NSQ NSCLC, are summarised in Table 14.

** Mitchell PL, Thursfield VJ, *et al.* Lung cancer in Victoria: are we making progress? *Med J Aust.* 2013; 199 (10):674-9.

Table 14: Estimated use and financial implications^a

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	■ ^b	■	■	■	■	■
No. of scripts dispensed	■	■	■	■	■	■
Estimated financial implications of atezolizumab + bevacizumab, proposed effective price						
Cost to PBS/RPBS	\$■	\$■	\$■	\$■	\$■	\$■
Copayments	\$■	\$■	\$■	\$■	\$■	\$■
Cost to PBS/RPBS less copayments	\$■	\$■	\$■	\$■	\$■	\$■
Estimated financial implications for later-line immunotherapy, pemetrexed and docetaxel						
Cost to PBS/RPBS	-\$■	-\$■	-\$■	-\$■	-\$■	-\$■
Copayments	-\$■	-\$■	-\$■	-\$■	-\$■	-\$■
Cost to PBS/RPBS less copayments	-\$■	-\$■	-\$■	-\$■	-\$■	-\$■
Net financial implications						
Net cost to PBS/RPBS	\$■	\$■	\$■	\$■	\$■	\$■
Net cost to MBS	\$■	\$■	\$■	\$■	\$■	\$■
Net cost to PBS/RPBS/MBS	\$■	\$■	\$■	\$■	\$■	\$■

^a A minor calculation error in determination of the number of Stage IV ALK+ non-squamous NSCLC patients was corrected during the evaluation. The corrected estimates are presented. The PSCR (p4) agreed with the correction of the stage IV (metastatic) non-squamous NSCLC ALK patients

^b Includes ■ grandfathered patients

Source: Table 4.16, p245; Table 4.28 p251, Table 4.29 p252, Table 4.45 p263, Table 4.54 p268 and Table 4.55 p269 of the submission; Excel workbook 'Section 4 workbook', supplied with the submission.

- 6.63 Patients with either activating mutations of the EGFR gene or an ALK gene rearrangement represented approximately ■% of the submission's estimated number of patients to be treated with atezolizumab + bevacizumab + PDC.
- 6.64 Univariate sensitivity analyses indicated that the financial implications to the PBS/RPBS were sensitive to the proportion of NSCLC patients with metastatic disease and the uptake of atezolizumab + bevacizumab + PDC.
- 6.65 The revised financial implications related to the revised rebate proposed in the Pre-PBAC Response maintained the estimated number of patients in year 6 at less than 10,000 patients and reduced the net cost to the PBS/RPBS in year 6 from \$30 - \$60 million to \$20 - \$30 million. Overall, the estimated net cost to the PBS/RPBS reduced to more than \$100 million over six years.
- 6.66 The PBAC considered the predicted low rate of uptake in EGFR/ALK negative patients to be particularly uncertain, but noted that this uncertainty could be managed by including this listing in the current immunotherapy NSCLC deed and cap arrangements.
- 6.67 The PBAC considered the assumed increase in the number of patients treated in the first line setting compared to the second line setting should be consistent with its recommendation from July 2018 for pembrolizumab, adjusted to incorporate the EGFR/ALK mutation positive population (estimated to be 16% of NSCLC patients). In other words, the majority of patients who will be treated under the proposed listing

will already be eligible for treatment under one of the current immunotherapy listings. The PBAC therefore considered the financial impact of listing as calculated by the submission to be an overestimate.

Financial Management – Risk Sharing Arrangements

- 6.68 The submission stated that the sponsor expressed its willingness to enter a confidential risk-sharing arrangement (RSA) with the Commonwealth. The pre-PBAC response stated the sponsor is willing to manage the financial uncertainty through the existing immunotherapy NSCLC expenditure caps if the expected net cost to the PBS/RPBS is added to the existing cap.
- 6.69 The PBAC considered that the uncertainty regarding uptake rates and financial impact should be managed by including the atezolizumab first line listing in the current RSA for immunotherapies in NSCLC.
- 6.70 The PBAC noted the current and projected caps in the immunotherapy expenditure caps for NSCLC (Table 15).

Table 15: Current cancer immunotherapy expenditure caps for NSCLC

Current caps					Projected ¹	
Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
N/A ²	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

1. Projected caps assume 1.5% population growth
 2. Year 1 cap has not been included as year 1 of deed has been completed and as it does not encompass all current listing
 Source: current cancer immunotherapy RSA for NSCLC

Committee-In-Confidence information



End Committee-In-Confidence information

- 6.72 The PBAC further noted the Department’s advice that current expenditure for immunotherapies in NSCLC is 30%-40% lower than envisaged when these caps were established, and agreed with the Department it is reasonable to conclude the expected expenditure for atezolizumab could likely be accommodated within these caps.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy - Public and Private Hospital) Authority Required (STREAMLINED) listing of atezolizumab and bevacizumab in combination with platinum doublet chemotherapy (PDC), for the first line treatment of patients with stage IV metastatic non-squamous (NSQ) non-small

cell lung cancer (NSCLC) on the basis that it should be available only under special arrangements under the Section 100 (Efficient Funding of Chemotherapy) Program. The PBAC recommended the special arrangements and circumstances described in the tables in section 8 below.

- 7.2 The PBAC was satisfied that atezolizumab + bevacizumab in combination with PDC provides, for some patients, a significant improvement in efficacy over PDC, or, for patients with PDL1 TPS \geq 50%, EGFR/ALK negative, NSQ disease, that atezolizumab + bevacizumab in combination with PDC will deliver similar clinical outcomes to pembrolizumab followed by chemotherapy.
- 7.3 The PBAC recommended the listing and restrictions proposed in the submission with amendments proposed by the secretariat to reflect the need for stable or responding disease for continuing treatment, or the need for progressive disease following treatment with TKIs in the EGFR mutant/ALK positive population. The PBAC recommended the inclusion of a grandfathering restriction as proposed by the submission, with the secretariat suggested changes. The PBAC noted the PSCR indicated that ■ patients were receiving treatment through a sponsor program and would need grandfathering onto PBS subsidy.
- 7.4 The PBAC considered that identifying the place of atezolizumab with bevacizumab within the current treatment algorithm for NSQ NSCLC was complex and changing rapidly with the availability of newer treatment options. However, the PBAC considered that there was a high clinical need for new treatment options for this patient group, particularly in the EGFR mutant/ALK positive subgroup post TKI therapy population, which was estimated to be the population with highest uptake in the submission.
- 7.5 The PBAC considered that the appropriate main comparator for the submission was PDC followed by PD-(L)1 therapy, as this is the therapy most likely to be replaced in practice for patients with a PD-L1 TPS $<$ 50%. The PBAC considered that for the EGFR mutant/ALK positive population, nivolumab and atezolizumab can be used in patients who have progressed on or after treatment with targeted therapies and therefore use of PDC followed by PD-(L)1 was also an appropriate comparator in this population. The PBAC considered pembrolizumab monotherapy followed by PDC was an appropriate comparator for the EGFR wild type/ALK negative PD-L1 \geq 50% NSQ population.
- 7.6 The PBAC noted the submission did not include relevant trials using PDC combinations other than CP. The PBAC considered the use of CP as a surrogate for all PDC to be reasonable, however noted that the submission should more appropriately have included all trials using PDC as a comparator arm, not solely those using CP. The PBAC noted that although still favourable, the HR was higher, suggesting a smaller effect on OS, with the inclusion of all PDC trials.
- 7.7 The PBAC noted the IMpower150 study comparing atezolizumab + bevacizumab + CP to bevacizumab + CP found a median overall survival (OS) benefit of 4.9 months with a hazard ratio (HR) of 0.76. The PBAC noted that the ESC identified that the assumption

of proportional hazards may not be valid given the survival curves for the treatments do not separate until 8 months and considered the HR should be interpreted with caution. The PBAC noted a median PFS benefit of 1.6 months and also noted that PFS is often not reliable for immunotherapy drugs such as PD-(L)1 inhibitors due to tumour flare and that OS data is considered a more reliable measure of benefit.

- 7.8 The PBAC noted that although the evidence was limited for the EGFR mutation/ALK positive population, there was evidence of a benefit in this group.
- 7.9 The PBAC considered the ITCs presented in the submission supported a PFS and OS benefit for atezolizumab + bevacizumab + PDC vs PDC for the EGFR wildtype/ALK negative and the EGFR mutant/ALK positive population, however considered that the results were uncertain due to transitivity issues and, in the case of the EGFR mutant/ALK positive group, the small subgroup studied.
- 7.10 The PBAC considered the IMpower150 study demonstrated the magnitude of additional benefit for atezolizumab + bevacizumab + CP (quadruple therapy) compared to atezolizumab + CP (triple therapy) was small and there were additional toxicities associated with the addition of bevacizumab. However, the PBAC noted the TGA Delegate had only recommended approval for atezolizumab in combination with bevacizumab. The PBAC considered that the incremental value of the inclusion of bevacizumab remained uncertain and indicated it will review further data from ongoing clinical trials, including IMpower132 when available, to determine the appropriateness of the quadruple therapy versus a triple therapy listing that excludes bevacizumab. The PBAC did not consider the change from a quadruple therapy listing to a triple therapy listing would substantially change uptake of atezolizumab in the first-line setting.
- 7.11 The PBAC considered the claim that atezolizumab + bevacizumab + PDC has non-inferior effectiveness and inferior safety compared with pembrolizumab monotherapy in patients with EGFR wild type/ALK negative NSQ NSCLC with high PD-L1 expression to be uncertain but reasonable, and noted that the toxicities were likely to be manageable in practice.
- 7.12 The PBAC agreed with the ESC that the survival curves in the economic model should converge at 7.5 years, with convergence commencing at 5 years. The PBAC noted the key uncertainties in the model were the treatment effect and the uncertain impact of changing the proportion of use of subsequent PD-(L)1 inhibitors post-progression.
- 7.13 The PBAC noted the Pre-PBAC Response offered an additional ■■■% rebate for atezolizumab when used in combination with bevacizumab + PDC resulting in an ICER of \$45,000 - \$75,000 per QALY in the cost-effectiveness analysis. On balance, the PBAC considered that, although uncertain, this ICER was reasonable and was consistent with previous considerations of similar NSCLC listings. The Committee also considered that on balance the cost-effectiveness of atezolizumab + bevacizumab + PDC is likely to be similar across the patient populations proposed in the submission. Therefore the PBAC was of the view that the cost of treatment with the atezolizumab + bevacizumab

components of the quadruple therapy should not exceed the cost of pembrolizumab monotherapy for any patient group receiving treatment for stage IV metastatic non-squamous (NSQ) non-small cell lung cancer (NSCLC).

- 7.14 The PBAC considered that the number of eligible patients should be aligned with previous understanding of this population, however considered the proposed uptake in the submission highly uncertain. In particular, the PBAC considered that estimates of uptake by █% by the PD-L1 ≥50% subgroup and █% in the broader EGFR wild type/ALK negative population were likely underestimates. The estimates of use in the EGFR mutant/ALK positive population were reasonable.
- 7.15 The PBAC considered that the residual uncertainty around uptake and financial impact would need to be managed within the current risk share arrangement and expenditure caps in place for immunotherapy medicines for NSCLC. The Committee considered that the modest increase in patient numbers likely to result from this listing was unlikely to require a revision of the RSA for NSCLC as current expenditure is tracking 30%-40% lower than envisaged when these caps were established.
- 7.16 The PBAC advised that atezolizumab + bevacizumab is not suitable for prescribing by nurse practitioners.
- 7.17 The PBAC recommended that the Early Supply Rule should not apply as this is a Section 100 listing.
- 7.18 The PBAC recalled its advice to the Minister in late 2018, recommending examination of the potential for a broad PBS subsidy listing for PD-(L)1 inhibitors for NSCLC, as substantial evidence and experience is now available for four PD-(L)1 medicines in this setting^{††}.
- 7.19 The PBAC noted that this is a complex restriction.
- 7.20 The PBAC noted that this submission is not eligible for an Independent Review as it has received a positive recommendation.

Outcome:

Recommended

^{††} Public Summary Document, Pembrolizumab, November 2018

8 Recommended listing

8.1 Add new items:

Atezolizumab

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Proprietary name and manufacturer
ATEZOLIZUMAB 1,200 mg/20 mL injection, 1 x 20 mL vial	1,200 mg	Initial: 5 Continuing:7	Tecentriq Roche Products Pty Ltd

atezolizumab - initial treatment for EGFR wild type/ALK negative patients

Category / Program	Section 100 – Efficient funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
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
Restriction Level / Method:	<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
Treatment criteria:	Patient must be undergoing combination treatment with bevacizumab and platinum-doublet chemotherapy.
Clinical criteria:	The condition must be non-squamous type non-small cell lung cancer (NSCLC), AND Patient must not have been treated for this condition in the metastatic setting, AND Patient must have a WHO performance status of 0 or 1, AND The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation or an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.
Administrative Advice	No increase in the maximum number of repeats may be authorised. 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. Special pricing arrangements apply.

atezolizumab - initial treatment for EGFR mutant/ALK positive patients

Category / Program	Section 100 – Efficient funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
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
Restriction Level / Method:	<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
Treatment criteria:	Patient must be undergoing combination treatment with bevacizumab and platinum-doublet chemotherapy.
Clinical criteria:	The condition must be non-squamous type non-small cell lung cancer (NSCLC), AND Patient must have a WHO performance status of 0 or 1, AND Patient must have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation or of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, AND Patient must have progressive disease following treatment with an epidermal growth factor receptors (EGFR) OR anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKI), 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 this condition.
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. No increase in the maximum number of repeats may be authorised. Special pricing arrangements apply.

atezolizumab - treatment continuation

Category / Program:	Section 100 – Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
Prescriber type:	Medical Practitioners

Public Summary Document – March 2019 PBAC Meeting

Severity:	Stage IV (metastatic)
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) NSCLC
Treatment phase:	Continuing treatment
Restriction Level / Method:	<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
Treatment criteria:	Patient must be undergoing combination treatment with bevacizumab until disease progression, unless not tolerated.
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug in this line of treatment, AND Patient must have stable or responding disease.
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special pricing arrangements apply.

bevacizumab

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Proprietary name and manufacturer
BEVACIZUMAB 100 mg/4 mL injection 400 mg/16 mL injection	1,800 mg 2 x 100 mg vials, 4 x 400 mg vials	Initial: 5 Continuing:7	Avastin Roche Products Pty Ltd

bevacizumab - initial treatment for EGFR wild type/ALK negative patients

Category / Program	Section 100 – Efficient funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
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
Restriction Level / Method:	<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

Public Summary Document – March 2019 PBAC Meeting

Treatment criteria:	Patient must be undergoing combination treatment with atezolizumab and platinum-doublet chemotherapy.
Clinical criteria:	The condition must be non-squamous type non-small cell lung cancer (NSCLC), AND Patient must not have been treated for this condition in the metastatic setting, AND Patient must have a WHO performance status of 0 or 1, AND The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation or an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special pricing arrangements apply.

bevacizumab - initial treatment for EGFR mutant/ALK positive patients

Category / Program	Section 100 – Efficient funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
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
Restriction Level / Method:	<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
Treatment criteria:	Patient must be undergoing combination treatment with atezolizumab and platinum-doublet chemotherapy.
Clinical criteria:	The condition must be non-squamous type non-small cell lung cancer (NSCLC), AND Patient must have a WHO performance status of 0 or 1, AND Patient must have evidence of an activating epidermal growth factor receptor (EGFR) gene or of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, AND Patient must have progressive disease following treatment with epidermal growth factor receptors (EGFR) OR anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKI), 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 this condition.

Public Summary Document – March 2019 PBAC Meeting

Administrative Advice	No increase in the maximum number of repeats may be authorised. Special pricing arrangements apply.
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bevacizumab - treatment continuation

Category / Program	Section 100 – Efficient funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
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
Restriction Level / Method:	<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
Treatment criteria:	Patient must be undergoing combination treatment with atezolizumab until disease progression unless not tolerated.
Clinical criteria:	The condition must be non-squamous type non-small cell lung cancer (NSCLC), AND Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not have disease progression while receiving PBS-subsidised treatment with this drug for this condition.
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special pricing arrangements apply.

**atezolizumab and bevacizumab
Grandfathering restriction**

Category / Program	Section 100 – Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required (STREAMLINED) Public Hospital Authority Required (STREAMLINED)
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:	Grandfathering treatment

Restriction Level / Method:	<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
Treatment criteria:	Patient must be undergoing combination treatment with bevacizumab and atezolizumab until disease progression unless not tolerated.
Clinical criteria:	<p>The condition must be non-squamous type non-small cell lung cancer (NSCLC), AND Patient must have previously received treatment with these drugs for this condition prior to [PBS listing date], AND Patient must have stable or responding disease, AND Patient must have a WHO performance status of 0 or 1.</p>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised.</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</p> <p>Special pricing arrangements apply.</p>

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

Roche welcomes the PBAC's decision to recommend atezolizumab and bevacizumab, for use in combination, for the treatment of patients with metastatic non-squamous non small cell lung cancer (NSCLC). Roche are working with the Department of Health towards a PBS listing at the earliest opportunity.