

5.02 ATEZOLIZUMAB, 1200 mg / 20 mL injection, 1 x 20 mL vial, Tecentriq®, Roche Products Pty Ltd

1 Purpose of application

- 1.1 Section 100 (Efficient Funding of Chemotherapy), Authority Required (STREAMLINED) listing for atezolizumab for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients who have disease progression on or after prior platinum based chemotherapy.
- 1.2 The requested listing was based on a cost-minimisation analysis of atezolizumab compared with nivolumab.

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

Component	Description
Population	Patients with locally advanced or metastatic NSCLC with a performance status of 0 or 1, who have progressed on or after treatment with platinum based chemotherapy
Intervention	Atezolizumab 1200 mg administered by IV infusion every three weeks until loss of clinical benefit*
Comparator	Nivolumab 3 mg/kg IV every two weeks until loss of clinical benefit*
Outcomes	Overall survival (OS) Duration of Response (DOR) Progression-free survival (PFS) [^] Safety
Clinical claim	Atezolizumab is non-inferior to nivolumab in terms of efficacy and safety in the treatment of locally advanced or metastatic NSCLC patients who have progressed on or after platinum-based chemotherapy.

NSCLC = non-small cell lung cancer; IV = intravenous.

* Loss of clinical benefit is defined in proposed PBS restrictions for atezolizumab and nivolumab as patients who no longer have stable or responding disease.

[^] The submission indicated that PFS as measured by RECIST 1.1 may not be adequate to characterise the anti-tumour activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions.

Source: Table 1.1.1, Section 1 of the submission.

2 Requested listing

- 2.1 Suggestions and additions are in italics and deletions are in strikethrough.

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Name, Restriction, Manner of administration and form	Max. amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
atezolizumab, 1200 mg/20 mL injection, 20 mL vial, 1	1200 mg	5	\$ [REDACTED] (Public, published) \$ [REDACTED] (Private, published) <i>Effective prices to be confirmed</i>	Tecentriq Roche Products Pty Ltd

Category / Program:	Section 100 – Efficient Funding of Chemotherapy
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:	Locally advanced or metastatic
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Locally advanced or metastatic NSCLC
Treatment phase:	<i>Initial treatment</i>
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must not have received prior treatment with a PD-1 (programmed cell death-1) inhibitor for this condition AND Patient must have a ECOG WHO performance status of 0 or 1 AND The treatment must be the sole PBS-subsidised therapy for this condition AND The condition must have progressed on or after prior platinum based chemotherapy.
Administrative Advice	<i>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.</i>

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Name, Restriction, Manner of administration and form	Max. amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
atezolizumab, 1200 mg/20 mL injection, 20 mL vial, 1	1200 mg	7	\$ [REDACTED] (Public, published) \$ [REDACTED] (Private, published) <i>Effective prices to be confirmed</i>	Tecentriq Roche Products Pty Ltd

Category / Program:	Section 100 – Efficient Funding of Chemotherapy
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:	Locally advanced or metastatic
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Locally advanced or metastatic NSCLC
Treatment phase:	<i>Continuing treatment</i>
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
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition AND The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have stable or responding disease.
Administrative Advice	<i>No increase in the maximum number of repeats may be authorised.</i>

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Name, Restriction, Manner of administration and form	Max. amount	№.of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
atezolizumab, 1200 mg/20 mL injection, 20 mL vial, 1	1200 mg	5	\$ [REDACTED] (Public, published) \$ [REDACTED] (Private, published) <i>Effective prices to be confirmed</i>	Tecentriq Roche Products Pty Ltd

Category / Program:	Section 100 – Efficient Funding of Chemotherapy
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:	Locally advanced or metastatic
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Locally advanced or metastatic NSCLC
Treatment phase:	<i>Grandfathering treatment</i>
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received treatment with this drug for this condition prior to [PBS listing date] AND The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have stable or responding disease AND Patient must have a <i>ECOG WHO</i> performance status of 0 or 1
Prescriber Instructions	<i>A patient may qualify for PBS-subsidised treatment under this restriction once only.</i>
Administrative Advice	<i>No increase in the maximum number of repeats may be authorised.</i>

- 2.2 The published dispensed price for maximum amount (DPMA) requested for atezolizumab is based on the equi-effective dose for a three weekly cycle of atezolizumab versus a two weekly cycle of nivolumab (cost-minimised using the published price for nivolumab).
- 2.3 Although the use of atezolizumab after targeted therapy is implied by the submission’s clinical management algorithm, it is not explicitly specified in the proposed listing of atezolizumab. This is inconsistent with the TGA approved indication which specifies that “in patients with tumour EGFR or ALK genomic aberrations, atezolizumab should be used after progression on or after targeted therapy”. However, the proposed listing is consistent with the current PBS listing of nivolumab for locally advanced or metastatic NSCLC patients who have progressed on or after prior chemotherapy.
- 2.4 One of the clinical criteria of the proposed PBS listing specifies that the patient must not have received prior treatment with a PD-1 inhibitor for this condition. The PBAC may wish to consider whether the restriction should be further refined to exclude patients who have received treatment with either a PD-1 or PD-L1 inhibitor. The PBS listing for nivolumab specifies that patients must not have received prior treatment with a PD-1 inhibitor. As such, the use of nivolumab (a PD-1 inhibitor) after treatment with atezolizumab (a PD-L1 inhibitor) would not be precluded under the proposed restriction criteria. The Pre-Sub-Committee Response (PSCR) (p4) agreed to the

inclusion of a restriction criterion excluding patients who had previously received a PD-1 or PD-L1 inhibitor, but stated that the same criterion should apply to nivolumab as well. The ESC noted the PSCR's comments, and advised that this criterion should be included in the proposed restriction for atezolizumab, and the current restriction for nivolumab should be updated to include this criterion as well.

- 2.5 The submission stated that a patient access program will be established for atezolizumab. The submission estimated that [REDACTED] patients will be on the access program and be eligible for grandfathering at the time of PBS listing (assumed April 2018).

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

3 Background

Registration status

- 3.1 TGA status: – Atezolizumab was approved by the TGA (on 27th July 2017) for the following indication:

Atezolizumab is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, atezolizumab should be used after progression on or after targeted therapy.

Previous PBAC consideration

- 3.2 This is the first submission of atezolizumab to the PBAC.

4 Population and disease

- 4.1 NSCLC represents the main histological type of lung cancer. For therapeutic purposes, NSCLC can be broadly categorised into two histologic subtypes: squamous (15%-25%) and non-squamous (75%-85%). Extent of disease is evaluated by staging, which determines the most appropriate form of treatment and prognosis.
- 4.2 In current practice, approximately 20% of patients would receive tyrosine kinase inhibitors (TKIs) first-line (targeting EGFR gene mutations or ALK translocations), followed by platinum-based chemotherapy upon progression, and subsequent nivolumab treatment. Patients with no EGFR or ALK mutations/translocations would initiate treatment with platinum-based chemotherapy, and subsequently receive nivolumab.
- 4.3 Atezolizumab is proposed for use in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC who have experienced disease progression on or after prior platinum based chemotherapy.
- 4.4 Atezolizumab is a humanised immunoglobulin monoclonal antibody that facilitates anticancer immune response through the binding to PD-L1. PD-L1 is an immune-checkpoint protein expressed on tumour cells and tumour infiltrating immune cells that, when activated, down regulates anti-tumour T-cell function by binding to PD-1

and B7.1 receptors. In contrast, the main comparator, nivolumab, is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production.

- 4.5 The proposed listing is for a patient population that is unselected based on PD-L1 expression. The TGA evaluator noted that overall, the results suggested that OS survival in patients treated with atezolizumab increases when patients with increased tumour cell (TC) and tumour-infiltrating immune cell (IC) PD-L1 expression are included in the treatment group. The TGA delegate raised an issue of whether the Product Information (PI) for atezolizumab should recommend PD-L1 testing in NSCLC, or given the apparent benefit in PD-L1 negative patients (in the atezolizumab trials), should this be left to clinician/patient choice. The Advisory Committee on Medicines (ACM) agreed that prognostic testing for PD-L1 expression in NSCLC is recommended, but not mandatory. The ACM also agreed that it would be reasonable for PD-L1 testing in NSCLC be left to the discretion of treating clinicians in the absence of robust and consistent data.
- 4.6 Although the clinical utility of the PD-L1 testing and the Royal College of Pathologists of Australasia (RCPA) Quality Assurance Program (QAP) are developing, and there is a lack of evidence for the appropriate PD-L1 expression threshold, these should not be considered as the basis for requesting an unselected population. This decision should be based primarily on clinical evidence showing that PD-L1 expression is not an effect modifier. The ESC considered that the utility of PD-L1 testing in this condition was a contentious matter, given that the sensitivity and specificity of the available tests were still an evolving area in molecular pathology. Additionally, noting that the current listing of nivolumab is not conditional on PD-L1 status, the ESC considered that, at the present time, it was difficult to determine if there was any benefit in stratifying patients based on PD-L1 status for atezolizumab (see paragraph 6.20).
- 4.7 Nivolumab was recommended for listing at the March 2017 PBAC meeting, and listed on the PBS in September 2017, for the treatment of patients with squamous or non-squamous locally advanced or metastatic NSCLC, after failure with a platinum-based chemotherapy. PBS-subsidised access to nivolumab is not dependent on PD-L1 status.

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

5 Comparator

- 5.1 The submission nominated nivolumab as the main comparator. This was appropriate given that nivolumab is a drug in the same therapeutic class as atezolizumab and has been listed on the PBS for the requested indication – locally advanced or metastatic NSCLC patients who have progressed on or after prior chemotherapy. The ESC and the PBAC considered that nivolumab was the appropriate comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2) via the Consumer Comments facility on the PBS website. The comments described the benefits of atezolizumab as an additional treatment option in NSCLC, and its efficacy and tolerability profile.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the atezolizumab submission, and advised that atezolizumab was comparable to nivolumab, which is currently PBS listed for this indication. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) of 5 for atezolizumab (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on a comparison against docetaxel.

Clinical trials

6.4 The submission was based on an indirect comparison of four randomised controlled trials (RCTs), via a common reference of docetaxel:

- OAK: A phase III open-label RCT of atezolizumab vs docetaxel in both squamous and non-squamous patients;
- POPLAR: A phase II open-label RCT of atezolizumab vs docetaxel in both squamous and non-squamous patients;
- Checkmate 017: A phase III open-label RCT of nivolumab vs docetaxel in squamous patients; and
- Checkmate 057: A phase III open-label RCT of nivolumab vs docetaxel in non-squamous patients.

6.5 Checkmate 017 and Checkmate 057 have been considered by the PBAC previously when considering nivolumab for locally advanced or metastatic NSCLC patients who have failed platinum-based chemotherapy.

6.6 The ITT populations from each of the arms in the respective trials were meta-analysed prior to conducting an indirect comparison, based on the Bucher method².

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

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

² Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol.* 1997;50(6):683-91. Epub 1997/06/01.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
OAK (Study GO28915)	<p>Primary Clinical Study Report – GO28915 OAK. A Phase III, open-label multicenter, randomised study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after failure with platinum-containing chemotherapy (OAK).</p> <p><u>Publications</u></p> <p>Rittmeyer A, Barlesi F et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial.</p> <p>Takada K, Toyokawa G, Okamoto T, et al. A Comprehensive Analysis of Programmed Cell Death Ligand-1 Expression With the Clone SP142 Antibody in Non-Small-Cell Lung Cancer Patients</p> <p>Gandara D, Von Pawel J. Atezolizumab Treatment Beyond Disease Progression in Advanced NSCLC: Results From the Randomized Ph III OAK Study.</p>	<p>Report No. 1070445. December 2016</p> <p>The Lancet 2017; 389: 255-265</p> <p>Clinical Lung Cancer. In Press. 2017 DOI:10.1016/j.clcc.2017.02.004</p> <p>Presented at ASCO 2017, Chicago Illinois, June 2017.</p>
POPLAR (Study GO28753)	<p>Primary Clinical Study Report – Protocol GO28753 – A Phase II, open-label, multicenter, randomised study to investigate the efficacy and safety of MPDL3280A (anti-PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after platinum failure.</p> <p>Supplementary Report for POPLAR CSR, corresponding to CCOD of 1 December 2015.</p> <p>Supplementary Report II (US) for POPLAR CSR, corresponding to CCOD of 1 December 2015.</p> <p><u>Publications:</u></p> <p>Fehrenbacher. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial</p> <p>Takada K, Toyokawa G, Okamoto T, et al. A Comprehensive Analysis of Programmed Cell Death Ligand-1 Expression With the Clone SP142 Antibody in Non-Small-Cell Lung Cancer Patients</p>	<p>Report No. 1065672 – December 2015</p> <p>POPLAR Supp 1069440 2016</p> <p>POPLAR Supp 1071999 2016 -</p> <p>The Lancet.2016 387 (10030):1837-1846</p> <p>Clinical Lung Cancer. In Press. 2017 DOI:10.1016/j.clcc.2017.02.004</p>
CHECKMATE-017	<p><u>Publications</u></p> <p>Brahmer J, Reckamp KL, Baas P et al. Nivolumab versus docetaxel in advanced squamous cell non-small cell lung cancer</p> <p>Barlesi F, Steins M, Horn, L et al. Long-term outcomes with nivolumab (Nivo) vs docetaxel (Doc) in patients (Pts) with advanced (Adv) NSCLC: CheckMate 017 and CheckMate 057 2-y update.</p> <p>Barlesi. Long-term outcomes with nivolumab versus docetaxel in patients with advanced NSCLC: Checkmate 017 and checkmate 057 2-year update. Asia-Pacific Journal of Clinical Oncology 12:115-116.</p>	<p>New England Journal of Medicine 2015; 373 (2):123-132.</p> <p>Annals of Oncology (abstract) 2016 27 (suppl_6) 1215PD-1215PD</p> <p>Asia-Pacific Journal of Clinical Oncology 12:115-116.2016</p>
CHECKMATE 057 (CA209-057)	<p>Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced non-squamous non-small-cell lung cancer.</p> <p>Barlesi F, Steins M, Horn, L et al. Long-term outcomes with nivolumab (Nivo) vs docetaxel (Doc) in patients (Pts) with advanced (Adv) NSCLC: CheckMate 017 and CheckMate 057 2-y update.</p> <p>Barlesi. Long-term outcomes with nivolumab versus docetaxel in patients with advanced NSCLC: Checkmate 017 and checkmate 057 2-year update. Asia-Pacific Journal of Clinical Oncology 12:115-116.</p>	<p>New England Journal of Medicine 2015; 373:1627-39</p> <p>Annals of Oncology (abstract) 2016 27 (suppl_6) 1215PD-1215PD</p> <p>Asia-Pacific Journal of Clinical Oncology 12:115-116.2016</p>

Source: Table 2.2.1, p7 Section 2 of the submission.

6.8 The key features of the randomised trials used in the indirect comparison are summarised in the table below.

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

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)
Atezolizumab vs. docetaxel					
OAK	850	R, OL 19 months	Low	Locally advanced or metastatic squamous and non-squamous NSCLC patients who have failed platinum-based chemotherapy	OS, PFS
POPLAR	287	R, OL 20 months ^a	Low	As above	OS, PFS
Meta-analysis	1137	Included OAK and POPLAR; ITT population; assessed OS			Survival gain
Nivolumab vs. docetaxel					
Checkmate 017	272	R, OL 18 months	Low	Locally advanced or metastatic squamous NSCLC patients who have failed platinum-based chemotherapy	OS, PFS ^b
Checkmate 057	582	R, OL 17 months	Low	Locally advanced or metastatic non-squamous NSCLC patients who have failed platinum-based chemotherapy	OS, PFS ^b
Meta-analysis	854	Include Checkmate 017 and Checkmate 057, ITT population, assessed OS			Survival gain

R = randomised; OL = open label; OS = overall survival; PFS = progression-free survival; NSCLC = non-small cell lung cancer; ITT = intention-to-treat.

^a updated analysis, Dec 2015 data cutoff

^b PFS was a specified secondary endpoint in all trials, however the reporting of PFS results for CHECKMATE 017 and CHECKMATE 057 is limited to data cuts of a minimum follow-up of 11 months and 13.2 months respectively.

Source: compiled during the evaluation using information from Sections 2.3 and 2.4 of the submission.

6.9 In the atezolizumab trials, randomisation was stratified according to histology, number of prior chemotherapy regimens and level of PD-L1 expression on immune cells (IC). In contrast, CHECKMATE 017 was stratified according to prior use of paclitaxel therapy (yes vs no) and geographic region. CHECKMATE 057 was stratified according to prior use of maintenance therapy (yes vs no) and number of prior therapies.

6.10 There were greater proportions of patients of Asian descent in the atezolizumab trials (OAK 21% and POPLAR 13%) compared to the nivolumab trials (approximately 2-3%). Although the measure of relative treatment effect in terms of OS did not appear to vary according to ethnicity, the median OS was higher for Asian patients than for Caucasian patients, in both the docetaxel and atezolizumab arms of both the POPLAR and OAK trials. This difference was substantially different in the OAK trial

[REDACTED]

[REDACTED]. This was likely to impact the transitivity of the trials. The PSCR (p2) contended that ethnicity was not a treatment effect modifier, as hazard ratios were consistent across ethnic subgroups, and therefore, ethnicity was unlikely to bias the hazard ratio for OS in the indirect comparison.

6.11 The PSCR (p1) acknowledged the inherent limitations of indirect comparisons, but argued that transitivity was not a significant issue in this case as the trials were of compatible design, with consistent eligibility criteria, and employed identical comparator treatment regimens (docetaxel). Additionally, key outcomes were

consistently defined, patients enrolled from countries with comparable health systems and conducted across a similar time period with similar methods of statistical analysis.

6.12 In the pooled data for the atezolizumab and nivolumab trials, there were a slightly lower proportion of patients with squamous histology in the atezolizumab trials (squamous: 28% in atezolizumab trials vs 32% in the nivolumab trials). Squamous histology is a negative prognostic factor for survival³.

Comparative effectiveness

6.13 Results for the whole trial populations relating to OS is provided in the table below.

Table 4: Whole trial population results for the outcome of overall survival

	OAK		POPLAR		CHECKMATE 017		CHECKMATE 057	
	ATZ	DOC	ATZ	DOC	NIVO	DOC	NIVO	DOC
Minimum follow up	19 months		20 months		18 months		17 months	
Time to event								
N (ITT)	425	425	144	143	135	137	292	290
Patients with event; n (%)	271 (63.8%)	298 (70.1%)	90 (62.5%)	110 (76.9%)	103 (76.3)	122 (89.1)	206 (70.5)	236 (80.8)
Median OS (months); (95% CI)	13.8 (11.8, 15.7)	9.6 (8.6, 11.2)	12.6 (9.7, 16.0)	9.7 (8.6, 12.0)	9.2 (7.3, 12.6)	6.0 (5.3, 7.4)	12.2 (9.7, 15.1)	9.4 (8.1, 10.7)
Stratified HR (95 %CI)	0.73 (0.62, 0.87)		0.69 (0.52,0.92)		0.62 (0.48, 0.81)		0.72 (0.60, 0.88) ^a	
p-value (log-rank)	0.0003		0.0106		0.0004		<0.001	
OS at 12 months								
Patients at risk; n (%)	218	151	70	55	57	32	146	111
Event-free rate % (95% CI)	54.70 (49.9, 59.6)	41.12 (36.2, 46.1)	51.6 (43.3, 59.9)	41.9 (33.5, 50.3)	42.1 (33.7, 50.3)	23.7 (16.9, 31.1)	51 (45-46)	39 (33-45)
OS at 18 months								
Patients at risk; n (%)	157	98	50	29	38	18	107	61
Event-free rate % (95% CI)	40.04 (35.2, 4.8)	26.9 (22.4, 31.4)	38.1 (30.0, 46.3)	24.5 (17.0, 31.9)	28.0 (NR, NR)	13.0 (NR, NR)	39 (34-45)	23 (19-28)

ATZ = atezolizumab; DOC = docetaxel; NIVO = nivolumab; OS = overall survival; ITT = intention to treat; CI = confidence interval; HR = hazard ratio; NR = not reported.

^a Proportional hazards assumption was not met.

Source: Table 2.5.1, Table 2.5.6, Table 2.5.11, and Table 2.5.14 of the submission.

6.14 The PBAC had previously noted that the key clinical trial, CHECKMATE 017, directly compared nivolumab and docetaxel, and that the risk of bias was low for the outcome

³ Cetin K, Ettinger DS, Hei Y-j, O'Malley CD. Survival by histologic subtype in stage IV non small cell lung cancer based on data from the Surveillance, Epidemiology and End Results Program. Clinical Epidemiology. 2011;3:139-48.

of OS (paragraph 7.5, 5.06. nivolumab Public Summary Document (PSD), March 2016 PBAC Meeting). At the February 2016 data cut-off (24 months minimum follow-up), only 6/137 (4%) patients in the docetaxel arm had crossed over to nivolumab treatment; the risk of bias was still considered to be low for OS.

- 6.15 The PBAC had previously noted that the proportional hazards assumption was not met in CHECKMATE 057, and that the nivolumab and docetaxel survival curves crossed with an initial increase and a subsequent decrease in hazard of death associated with nivolumab compared with docetaxel. Therefore, the estimated hazard ratio, as a measure of the relative treatment effect or reduction in risk, could not be relied upon given the measure's dependency on follow-up time. The PBAC therefore primarily relied on the statistically significant log rank test (which is not affected by these survival curves crossing) to accept the claim of superior comparative effectiveness (paragraph 7.6, nivolumab PSD, March 2016 PBAC Meeting).
- 6.16 The submission used time to event and OS rates (event-free rates) at 12 and 18 months outcomes as the basis for an indirect comparison of atezolizumab vs nivolumab.
- 6.17 The OS results by histology from each of the trials included in the indirect comparison are summarised below.

Table 5: Overall survival results, squamous histology

	OAK		POPLAR		CHECKMATE 017	
	ATZ	DOC	ATZ	DOC	NIVO	DOC
N	112	110	49	48	135	137
Patients with event; n (%)	81 (72.3%)	90 (81.8%)	32 (65.3)	42 (87.5)	103 (76.3)	122 (89.1)
Median OS (months); (95% CI)	8.9 (7.4, 12.8)	7.7 (6.3, 8.9)	10.1 (6.7, 14.5)	8.6 (5.4, 11.6)	9.2 (7.3, 12.6)	6.0 (5.3, 7.4)
Stratified HR (95 %CI)	0.73 (0.54, 0.98)		0.66 (0.41, 1.05)		0.62 (0.48, 0.81)	
p-value (log-rank)	0.038		0.075		0.0004	

ATZ = atezolizumab; NIVO = nivolumab; HR = hazard ratio; OS = overall survival.
Source: Table 2.6.8, Table 2.6.13, and Table 2.6.17 Section 2 of the submission.

Table 6: Overall survival results, non-squamous histology

	OAK		POPLAR		CHECKMATE 057	
	ATZ	DOC	ATZ	DOC	NIVO	DOC
N	313	315	95	95	292	290
Patients with event; n (%)	190 (60.7%)	208 (66.0%)	58 (61.1)	68 (71.6)	206 (70.5)	236 (81.4)
Median OS (months); (95% CI)	15.6 (13.3, 17.6)	11.2 (9.3, 12.6)	14.8 (9.8, 19.5)	10.9 (8.8, 13.6)	12.2 (9.7, 15.1)	9.4 (8.1, 10.7)
Stratified HR (95 %CI)	0.73 (0.60, 0.89)		0.69 (0.49, 0.98)		0.72 (0.60, 0.88) ^a	
p-value (log-rank)	0.002		0.039		<0.001	

ATZ = atezolizumab; NIVO = nivolumab; HR = hazard ratio; OS = overall survival.

. ^a Proportional hazards assumption was not met.

Source: Table 2.6.8, Table 2.6.13 and Table 2.6.19, Section 2 of the submission.

- 6.18 The submission argued that a difference in OS of 3 months was considered clinically meaningful in locally advanced and metastatic NSCLC. Using this criterion,

atezolizumab did not result in a clinically meaningful difference in OS over docetaxel for squamous patients (difference in median OS of 2.2 months in OAK, and 1.5 months in POPLAR). Nivolumab was associated with a difference in OS of 3.2 months in these patients, compared with docetaxel in CHECKMATE 017. However, the squamous population in the atezolizumab trials was a subgroup of the intention to treat population, and therefore the baseline characteristics of the two comparative arms within the trial might not be comparable. The ESC considered that small absolute differences in OS in the squamous populations could also be attributed to the poor prognosis of squamous NSCLC patients. As such, the clinical importance of an OS gain of this magnitude remains uncertain.

- 6.19 The ESC noted that, for non-squamous patients, there was a greater improvement in median OS of the immunotherapies compared with docetaxel, with all immunotherapy arms resulting in an improvement in OS of more than 3 months.
- 6.20 There was a trend towards greater treatment effect in those with higher levels of PD-L1 expression. This result, however, should be interpreted with caution, as the baseline characteristics by PD-L1 status were not balanced across the two arms in the atezolizumab trials, as randomisation was stratified using PD-L1 expression in immune cells alone (i.e. not the combination of expression on immune cells and tumour cells). Furthermore, comparison of treatment effect by PD-L1 expression status between atezolizumab and nivolumab was difficult to assess given the different PD-L1 tests utilised in the atezolizumab (Ventana SP142) and nivolumab trials (Dako 28-8) and the low level of concordance between the two assays (overall percentage of agreement, using 1% cut-off was 63.2%)⁴. Although atezolizumab's comparative effectiveness versus docetaxel was demonstrated in all subgroups tested, the ESC considered that the role of PD-L1-based stratification of subgroups remained unclear, for reasons discussed earlier (see paragraph 4.6). The Pre-PBAC response (p1) reiterated that the pivotal trial evidence for atezolizumab in previously treated NSCLC had clearly demonstrated a consistent and meaningful clinical benefit, regardless of PD-L1 expression.

⁴ Hirsch FR, McElhinny A, et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. *J Thorac Oncol.* 2017 Feb;12(2):208-22.

Table 7: OS by PD-L1 expression, OAK and POPLAR

	OAK		POPLAR	
	ATZ	DOC	ATZ	DOC
Minimum follow up	19 months		20 months	
TC3 or IC3				
N	72	65	24	23
Patients with event	37 (51.4%)	49 (75.4%)	12 (50.0%)	18 (78.3%)
Median OS (months); (95% CI)	20.5 (17.5, NE)	8.9 (5.6, 11.6)	NE (9.5, NE)	11.1 (6.7, 14.4)
Unstratified HR (95 %CI)	0.41 (0.27, 0.64)		0.45 (0.22, 0.95)	
p-value log rank	p<0.0001		0.033	
TC2/3 or IC2/3				
N	129	136	50	55
Patients with event	79 (61.2%)	92 (67.6%)	29 (58.0%)	46 (83.6%)
Median OS (months); (95% CI)	16.3 (13.3, 20.1)	10.8 (8.8, 12.7)	15.1 (8.4, NE)	7.4 (6.0, 12.5)
Unstratified HR (95 %CI)	0.67 (0.49, 0.90)		0.50 (0.31, 0.80)	
p-value log rank	0.008		0.003	
TC1/2/3 or IC1/2/3				
N	241	222	93	102
Patients with event	151 (62.7%)	149 (67.1%)	54 (58.1%)	78 (76.5%)
Median OS (months); (95% CI)	15.7 (12.6, 18.0)	10.3 (8.8, 12.0)	15.1 (11.0, NE)	9.2 (7.3, 12.8)
Stratified HR (95 %CI)	0.74 (0.58, 0.93)		0.59 (0.41, 0.83)	
p-value log rank	0.0102		0.003	
TC0 and IC0 (<1% expression in tumour and immune cells)				
N	180	199	51	41
Patients with event	116 (64.4%)	146 (73.4%)	36 (70.6%)	32 (78.0%)
Median OS (months); (95% CI)	12.6 (9.6, 15.2)	8.9 (7.7, 11.5)	9.7 (6.7, 12.0)	9.7 (8.6, 12.0)
Unstratified HR (95 %CI)	0.75 (0.59, 0.96)		0.88 (0.55, 1.42)	
p-value log rank	0.0215		0.601	

ATZ = atezolizumab; DOC = docetaxel; HR = hazard ratio; OS = overall survival.

IC0 = Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in ICs covering <1% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma.

IC1 = Presence of discernible PD-L1 staining of any intensity in ICs covering between ≥1% and <5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma.

IC2 = Presence of discernible PD-L1 staining of any intensity in ICs covering between ≥5% and <10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma.

IC3 = Presence of discernible PD-L1 staining of any intensity in ICs covering ≥10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma.

TC0 = Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in <1% TCs.

TC1 = Presence of discernible PD-L1 staining of any intensity in ≥1% and ≤5% TCs.

TC2 = Presence of discernible PD-L1 staining of any intensity ≥5% and <50%.

TC3 = Presence of discernible PD-L1 staining of any intensity in ≥50% TCs.

Source: Table 2.6.9 and Table 2.6.14, Section 2 of the submission.

6.21 Results of the indirect comparison in terms of OS (time to event data) are provided below. The results of this analysis should be interpreted with caution because the proportional hazards assumption did not hold for the outcome of OS in CHECKMATE 057. It was unclear whether this was the case with atezolizumab trials as well, as the submission did not provide a formal analysis of the proportional hazards assumption.

Table 9: Indirect comparison of atezolizumab with nivolumab, overall survival (18 months)

Dataset	Overall survival 18 months		
	OR (95% CI)	RR (95% CI)	RD (95% CI)
	Unadjusted (calculated from reported/published event counts)		
Atezolizumab vs docetaxel			
OAK	1.95 (1.45, 2.64)	1.60 (1.29, 1.98)	0.14 (0.08, 0.20)
POPLAR	2.09 (1.23, 3.56)	1.71 (1.15, 2.54)	0.14 (0.04, 0.25)
Nivolumab vs docetaxel			
CHECKMATE 017	2.59 (1.39, 4.82)	2.14 (1.29, 3.56)	0.15 (0.06, 0.24)
CHECKMATE 057	2.11 (1.47, 3.03)	1.69 (1.30, 2.18)	0.16 (0.08, 0.23)
Meta-analyses	Mantel-Haenszel random effects model, RevMan5.3		
Atezolizumab vs docetaxel			
OAK & POPLAR	██████████	██████████	██████████
Nivolumab vs docetaxel			
CHECKMATE 017 & CHECKMATE 057	██████████	██████████	██████████
Indirect comparisons	ITC Bucher method, CADTH calculator		
Atezolizumab vs nivolumab*			
OAK & POPLAR vs CHECKMATE 017 & CHECKMATE 057	██████████	██████████	██████████

OR = odds ratio; RR = relative risk; RD = risk difference; ITC = indirect treatment comparison; CADTH = Canadian Agency for Drugs and Technologies in Health.

* Numbers above 1 (OR, RR) or 0 (RD) favour atezolizumab.

Source: Table 2.6.3, Section 2 of the submission.

6.23 The submission did not provide an indirect comparison of atezolizumab vs nivolumab by histology. This analysis was conducted during the evaluation. Results are presented in the table below.

Table 10: Results of the indirect comparison of atezolizumab vs nivolumab by histology

Time to event (Overall survival)			
	Hazard ratio (95% CI)		
Squamous	██████████		
Non-squamous	██████████		
Overall survival rate at 12 months			
	OR (95% CI)	RR (95% CI)	RD (95% CI)
Squamous	██████████	██████████	██████████
Non-squamous	██████████	██████████	██████████
Overall survival rate at 18 months			
Squamous	██████████	██████████	██████████
Non-squamous	██████████	██████████	██████████

OR = odds ratio; RR = relative risk; RD = risk difference.

Source: Compiled during the evaluation, based on information presented in the submission.

6.24 The submission stated that an appropriate non-inferiority margin for the comparison of immunotherapies in NSCLC has not yet been established. The submission indicated that the PBAC has previously considered a comparison of immunotherapies for melanoma (nivolumab vs pembrolizumab), where the results of an indirect treatment comparison for OS, with a HR of 1.04 (0.70, 1.54) was accepted as a basis for non-inferiority. The submission requested that PBAC consider this past precedent for acceptance of non-inferiority for the current comparison of immunotherapies, considering the totality of evidence across key patient-relevant outcomes when

considering the clinical claims made in the submission. However, it should be noted that the confidence intervals of the OS rates from the indirect comparison at both 12 and 18 months contained differences that might be clinically meaningful (Table 9). Similar results were reported for the indirect comparisons by histology. Therefore, an inferior treatment effect of atezolizumab compared with nivolumab could not be ruled out.

6.24.1 The PSCR (p1) argued that inferior treatment effect of atezolizumab compared with nivolumab could indeed be ruled out, by presenting a scenario analyses which claimed that to assume inferiority, an input of pooled OS HR of [REDACTED] was required, in contrast to the observed pooled results from the trials of OS HR (95%CI) [REDACTED]. Additionally, the PSCR claimed that the odds ratio, relative risk and risk difference measures in the scenario analyses were outside the 95% CI for the actual observed pooled data for atezolizumab vs docetaxel. The PSCR therefore claimed that the results of this scenario analysis disproved the possibility of an inferior comparative effectiveness of atezolizumab, compared with nivolumab.

6.24.2 The ESC agreed with the PSCR's arguments and the results of the scenario analysis, and advised that the submission's claim of non-inferior comparative effectiveness compared with nivolumab was reasonable.

Comparative harms

6.25 A summary of the adverse events (AEs) observed in each of the respective atezolizumab and nivolumab trials are provided below.

Table 11: Summary comparison of adverse events across trials

Adverse event	Number of patients with event (%)							
	OAK (19 months)		POPLAR (13.3 months)		CHECKMATE 017 (11 months)		CHECKMATE 057 (13 months)	
	ATZ N=609	DOC N=578	ATZ N=142	DOC N=135	NIVO N=131	DOC N=129	NIVO N=287	DOC N=268
Any AE	573 (94.1)	555 (96)	136 (95.8)	130 (96.3)	127 (96.9)	125 (96.9)	280 (98)	265 (99)
Grade 3,4 AEs	227 (37.3)	324 (56.5)	57 (40.1)	71 (52.6)	9 (6.9)	20 (15.5)	132 (46)	180 (67)
SAEs	194 (31.9)	181 (31.3)	50 (35.2)	46 (34.1)	61 (46.6)	70 (54.3)	134 (46.7)	111 (41.4)
AEs leading to discontinuation	46 (7.6)	108 (18.7)	11 (7.7)	30 (22)	14 (10.7)	26 (20.2)	48 (16.7)	58 (21.6)
AEs leading to dose modification/ interruption	152 (25)	210 (36.3)	15 (10.6)	32 (23.7)	NR	NR	NR	NR
AESIs (any causality)	184 (30.2)	132 (22.8)	41 (28.9)	40 (29.6)	NR	NR	NR	NR
Treatment-related select AEs	NR	NR	NR	NR	42 (32.1)	46 (35.7)	186 (64.8)	129 (48.1)
	OAK (19 months)		POPLAR (13.3 months)		CHECKMATE 017 (24 months)		CHECKMATE 057 (24 months)	
Treatment-related AEs	390 (64.0)	496 (85.8)	95 (66.9)	119 (88.1)	80 (61)	112 (87)	204 (71)	236 (88)
Treatment-related Grade 3,4 AEs	90 (14.8)	248 (42.9)	16 (11.3)	52 (38.5)	10 (8)	72 (56)	32 (11)	145 (54)
Treatment-related SAEs	63 (10.3)	102 (17.6)	12 (8.5)	23 (17.0)	NR	NR	NR	NR
Treatment-related deaths	0	1 (0.2)	1 (0.7)	3 (2.2)	0	3 (2)	1 (<1)	1 (<1)

AE = adverse event, SAE = serious adverse event; AESI = adverse event of special interest; ATZ = atezolizumab; DOC = docetaxel; NR = not reported.

Source: Table 2.6.5, Section 2 of the submission.

6.26 In the individual trials, immunotherapy generally resulted in fewer adverse events than the use of docetaxel chemotherapy. The submission did not conduct a formal indirect comparison between the immunotherapies for safety.

6.27 A higher rate of AEs leading to discontinuation was observed in CHECKMATE 057 for nivolumab compared with atezolizumab in both OAK and POPLAR. The rate of AEs leading to discontinuation in the docetaxel arms across the trials was similar.

Interpretation of clinical evidence

6.28 The clinical claim made by the submission was that atezolizumab is non-inferior in terms of both effectiveness and safety compared to the primary comparator, nivolumab.

6.29 The submission did not specify a non-inferiority margin for the indirect comparison. However, the confidence intervals of the OR, RR and RD from the indirect comparison at both 12 and 18 months contained differences that might be clinically meaningful. Therefore, an inferior treatment effect of atezolizumab compared with nivolumab could not be ruled out. The PSCR (p1) claimed that atezolizumab's inferiority to nivolumab was statistically implausible, using a scenario analysis (see paragraph 6.24.1). The ESC agreed with the PSCR's arguments and the results of the scenario analysis, and advised that the submission's claim of non-inferior comparative effectiveness compared with nivolumab was reasonable.

- 6.30 The ESC considered that, despite the differences between the atezolizumab and nivolumab trials, the incidence and severity of AEs were similar with both immunotherapy treatments. As such, the ESC advised that the submission's claim of non-inferior safety compared with nivolumab was reasonable.
- 6.31 The PBAC considered that the submission's claim of non-inferior comparative effectiveness compared with nivolumab was reasonable.
- 6.32 The PBAC considered that the submission's claim of non-inferior comparative safety compared with nivolumab was reasonable.

Economic analysis

- 6.33 The equi-effective doses were proposed as 1200 mg atezolizumab every 3 weeks and 360 mg nivolumab every 3 weeks (i.e. calculated as 240 mg nivolumab administered every two weeks multiplied by $3/2$, with the 240 mg dose of nivolumab per infusion calculated based in the average weight of patients in the nivolumab studies rounded up to the most efficient selection of vial sizes being 2x100 mg vials plus 1x40 mg vial). The equi-effective doses were consistent with the target doses in the clinical trials. None of the trials allowed dose reductions for either atezolizumab or nivolumab. The submission assumed equivalent treatment durations for both atezolizumab and nivolumab. It was unclear whether this assumption was appropriate, due to transitivity issues between trials, and incomplete follow up data for the nivolumab submissions. The ESC considered that the equi-effective doses proposed in the submission were reasonable, however there were inherent uncertainties in the comparative durations of treatment, as this was informed by results of an indirect comparison. The Pre-PBAC response (p1) maintained that it was appropriate to assume equivalent treatment durations for atezolizumab and nivolumab, as there was no evidence to suggest a significant difference in the treatment durations between the two agents.
- 6.34 The submission has also estimated a small cost saving associated with the reduced dosing frequency of atezolizumab (every three weeks) compared to nivolumab (every two weeks). The submission requested that the difference in administration costs (\$32.53/administration) be included in the calculation of the effective price of atezolizumab from the effective price of nivolumab, so that price parity is inclusive of both drug and administration costs at the effective price.
- 6.35 The results of the cost-minimisation analysis are provided in the table below.

Table 12: Cost-minimisation analysis: atezolizumab versus nivolumab

Variable	Atezolizumab			Nivolumab		
Drug cost (published ex-manufacturer price) per administration						
Dose per administration	1200 mg			240 mg*		
Vials	Unit (mg)	AEMP	# vials	Unit (mg)	AEMP	# vials
	1200	7,476.30	1	40	\$830.70	1
				100	\$2,076.75	2
List AEMP per administration	\$7,476.30			\$4,984.20		
Equi-effective dose						
Administrations per 3 weekly cycle	1.00			1.50		
Equi-effective dose per 3 weekly cycle	1200 mg			360 mg		
Drug cost (ex-manufacturer price) per 3 weekly cycle at equi-effective dose						
Total drug cost per 3 weekly cycle	\$7,476.30			\$7,476.30		
Incremental drug cost per 3 weekly cycle (atezolizumab vs nivolumab)				\$0		
Administration cost						
Number of IV administrations per 3 weekly cycle	1			1.5		
Cost per administration (MBS Item 13915)				\$65.05		
Total administration cost per 3 weekly cycle	\$65.05			\$97.58		
Incremental administration cost per 3 weekly cycle (atezolizumab vs nivolumab)				-\$32.53		
Total cost (cost-minimisation)						
Total drug and administration cost per 3 weekly cycle	\$7,443.78			\$7,573.88		
Total incremental cost per 3 weekly cycle (atezolizumab vs nivolumab)				-\$32.53		

AEMP = approved ex-manufacturer price; MBS = Medical Benefits Scheme; IV = intravenous.

* As per nivolumab November 2016 PSDs.

Source: Table 3B.4.1, Section 3 of the submission.

6.36 The submission acknowledged that the PBAC outcomes statement for nivolumab suggest that Risk Sharing Arrangements have been proposed to address the uncertainty raised by PBAC in its November 2016 deferral of nivolumab. Given that the sponsor did not know the effective price for nivolumab, the cost-minimisation presented in the submission used the published price of nivolumab. This analysis was presented based on a request the effective price for atezolizumab would be no higher than the cost-minimised effective price for nivolumab (also reflecting the difference in the frequency of administration) for patients with locally advanced or metastatic NSCLC, who have progressed on or after platinum-based chemotherapy.

Drug cost/patient/course: \$ [REDACTED]

6.37 This calculation is based on a dose of 1200 mg every three weeks, and an average of [REDACTED] administrations over an average treatment duration of [REDACTED] months (based on an extrapolation of trial data). This was based on a weighted DPMA of \$7,681.59, with a 14.5%:85.5% split between public and private hospital dispensing as per the nivolumab submissions. The DPMA was based on the published ex-manufacturer price of nivolumab, and the cost-minimised price of atezolizumab as estimated in Table 10.

Estimated PBS usage & financial implications

6.38 This submission was not considered by DUSC. The submission used a mixed-method approach to estimate the expected utilisation and financial estimates of listing atezolizumab. An epidemiological approach was used to estimate the number of patients eligible to be treated under the proposed restriction for atezolizumab and for

nivolumab, and then a proportional market share approach (based on clinical advice) was used to estimate the relative treatment uptake of nivolumab and atezolizumab. This approach was appropriate, given the absence of market data for nivolumab.

6.39 The estimated use and financial implications is provided in the table below.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	████	████	████	████	████	████
Atezolizumab: number of scripts dispensed ^a	██████	██████	██████	██████	██████	██████
Nivolumab: number of scripts dispensed ^b	████	████	████	████	████	████
Estimated financial implications of atezolizumab						
Cost to PBS/RPBS	████████	████████	████████	████████	████████	████████
Copayments	████████	████████	████████	████████	████████	████████
Cost to PBS/RPBS less copayments	████████	████████	████████	████████	████████	████████
Estimated financial implications for nivolumab (reduction in use)						
Cost to PBS/RPBS	████████	████████	████████	████████	████████	████████
Copayments	████████	████████	████████	████████	████████	████████
Cos savings to PBS/RPBS less copayments	████████	████████	████████	████████	████████	████████
Net financial implications						
Net cost to PBS/RPBS	████████	████████	████████	████████	████████	████████
Net cost to MBS	████████	████████	████████	████████	████████	████████
Net cost to other gov't health budgets (TGA-licensed compounders fee)	████████	████████	████████	████████	████████	████████
Combined net cost to PBS/RPBS/MBS/other	████████	████████	████████	████████	████████	████████

^a Assuming █████ scripts per course as estimated by the submission, for an average treatment duration of █████ months.

^b Assuming █████ scripts per course as estimated by the submission, for an average treatment duration of █████ months.

Source: Compiled during the evaluation based on information provided in 'Section 4 Workbook.xlsx'.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net saving to Government would be less than \$10 million per year.

6.40 The approach used by the submission appeared to be reasonable. The financial estimates were most sensitive to the uptake rate, given the small cost saving associated with reduced treatment frequency (in terms of both dispensing fees and reduced administration costs), which would be eliminated if the price of atezolizumab is adjusted for these differences as requested by the submission.

6.41 The ESC considered that there would be a risk of leakage to patients with worse performance status than ECOG 0-1. However, the ESC acknowledged that this risk applied to the current listing of nivolumab as well.

Quality use of medicines

6.42 As recommended by the TGA, the sponsor indicated its willingness to perform additional activities to minimise the risk of immune-related adverse events and infusion-related reactions, through the provision of educational materials (including a Health Care Professional brochure and patient alert card). The objective of these materials will enable early recognition and prompt management. A similar implementation program applied to the registration of nivolumab.

Financial management – risk sharing arrangements

6.43 The submission noted that from the PBAC outcomes statement for nivolumab that Risk Sharing Arrangements have been proposed to address uncertainties raised by PBAC in its November 2016 deferral of nivolumab. The submission claimed that the PBS listing of atezolizumab will not result in additional uncertainty to Government health budgets beyond that pertaining to nivolumab's existing arrangement.

6.44 Special Pricing Arrangements apply to the listing of nivolumab. The sponsor has accepted that the effective price for atezolizumab would therefore be based on the effective price for nivolumab.

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 for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients who have disease progression on or after prior platinum based chemotherapy. In making this recommendation, the PBAC considered that atezolizumab was non-inferior in effectiveness and safety compared with nivolumab, which is currently listed on the PBS for this population.

7.2 The PBAC considered that the requested restriction was appropriate as modified by the Secretariat, and advised that patients who received prior treatment with either a PD-1 inhibitor or a PD-L1 inhibitor should be excluded from accessing initial treatment with atezolizumab via the PBS. The PBAC advised that a flow-on change to the nivolumab restriction was also warranted in order to exclude patients who have received treatment with either a PD-1 inhibitor or a PD-L1 inhibitor.

7.3 The PBAC noted that nivolumab, a PD-1 inhibitor, was the first immunotherapy listed on the PBS as second line therapy for advanced NSCLC following chemotherapy, regardless of PD-L1 expression. The PBAC noted that although atezolizumab was a PD-L1 inhibitor, it was similar in action to nivolumab, and therefore the submission's proposed place in clinical therapy was appropriate. Noting that the current listing of nivolumab is not conditional on PD-L1 expression status and the weakness of any signal for the effectiveness of atezolizumab to vary substantially by PD-L1 expression, the PBAC advised that, at the present time, there was no basis to recommend stratifying patients based on PD-L1 expression status for atezolizumab.

7.4 The PBAC advised that nivolumab was the appropriate comparator.

- 7.5 The PBAC noted that the submission was based on an indirect comparison of four randomised controlled trials (OAK (n=850) and POPLAR (n=287) for atezolizumab, Checkmate 017 (n=272) and Checkmate 057 (n=582) for nivolumab) with PFS and OS as outcomes, via a common reference arm involving docetaxel. The PBAC considered that the OAK and POPLAR trials provided sufficient evidence of an overall survival gain for atezolizumab over docetaxel. The PBAC noted that the submission also presented outcomes of subgroups of the OAK and POPLAR trials stratified by squamous and non-squamous histologies and by PD-L1 expression status. The PBAC considered that these analyses did not provide a clear basis for limiting any PBS restriction for atezolizumab by histology or PD-L1 expression status. Notwithstanding these issues and other inherent limitations of indirect comparisons, the PBAC advised that the submission's claim of non-inferior comparative effectiveness compared with nivolumab was reasonable.
- 7.6 The PBAC considered that atezolizumab was superior in safety compared to docetaxel, and had a similar safety profile compared to nivolumab. Overall, the PBAC considered that the submission's claim of non-inferior safety compared to nivolumab was reasonable.
- 7.7 The PBAC considered that the submission's proposed equi-effective doses of 1200 mg atezolizumab every 3 weeks and 360 mg nivolumab every 3 weeks (i.e. calculated as 240 mg nivolumab administered every two weeks multiplied by 3/2, with the 240 mg dose of nivolumab per infusion calculated based in the average weight of patients in the nivolumab studies rounded up to the most efficient selection of vial sizes being 2x100 mg vials plus 1x40 mg vial) had a reasonable basis, noting that (i) they were consistent with the doses in the respective clinical trials of the two agents; and (ii) identical durations of treatment were assumed for atezolizumab and nivolumab. However, the PBAC also advised that the cost-minimisation approach would need to reflect the relevant pricing and risk-sharing arrangements applicable to the nivolumab listing in NSCLC.
- 7.8 The PBAC advised that the financial estimates presented in the submission were appropriate (after adjusting for the average dose rather than the maximum dose of nivolumab), but noted that the small cost saving associated with reduced treatment frequency (in terms of both dispensing fees and reduced administration costs), would be eliminated if the price of atezolizumab is adjusted for these differences as requested by the submission. As such, the PBAC also advised that atezolizumab should join the nivolumab risk-share agreement in order to ensure cost-neutrality to the Commonwealth.
- 7.9 The PBAC advised that atezolizumab should be exempt from the Early Supply Rule.
- 7.10 The PBAC advised that atezolizumab should not be prescribed by nurse practitioners as antineoplastic agents are currently out of scope for prescribing by nurse practitioners.
- 7.11 The PBAC recommended that atezolizumab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review because it has received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. amount	No. of Rpts	Proprietary Name	Manufacturer
atezolizumab, 1200 mg/20 mL injection, 20 mL vial, 1	1200 mg	5	Tecentriq	Roche Products Pty Ltd

Category / Program:	Section 100 – Efficient Funding of Chemotherapy
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:	Locally advanced or metastatic
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Locally advanced or metastatic NSCLC
Treatment phase:	Initial treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition AND Patient must have a-WHO performance status of 0 or 1 AND The treatment must be the sole PBS-subsidised therapy for this condition AND The condition must have progressed on or after prior platinum based chemotherapy.
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.

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Name, Restriction, Manner of administration and form	Max. amount	№.of Rpts	Proprietary Name	Manufacturer
atezolizumab, 1200 mg/20 mL injection, 20 mL vial, 1	1200 mg	7	Tecentriq	Roche Products Pty Ltd

Category / Program:	Section 100 – Efficient Funding of Chemotherapy
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:	Locally advanced or metastatic
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Locally advanced or 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
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be the sole PBS-subsidised treatment for this condition AND Patient must have stable or responding disease.
Administrative Advice	No increase in the maximum number of repeats may be authorised.

Name, Restriction, Manner of administration and form	Max. amount	№.of Rpts	Proprietary Name	Manufacturer
atezolizumab, 1200 mg/20 mL injection, 20 mL vial, 1	1200 mg	5	Tecentriq	Roche Products Pty Ltd

Category / Program:	Section 100 – Efficient Funding of Chemotherapy
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:	Locally advanced or metastatic
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Locally advanced or metastatic NSCLC
Treatment phase:	Grandfathering treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received treatment with this drug for this condition prior to [PBS listing date] AND The treatment must be the sole PBS-subsidised treatment for this condition AND Patient must have stable or responding disease
Prescriber Instructions	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.
Administrative Advice	No increase in the maximum number of repeats may be authorised.

8.2 Flow-on restriction changes:

The initial treatment criteria for nivolumab for the treatment of NSCLC (11143L and 11158G) should be amended to replace the criterion:

‘Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor for this condition’

with the following criteria:

‘Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition’

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 for patients with locally advanced or metastatic NSCLC and are working with the Department of Health towards a PBS listing at the earliest opportunity.