

6.02 ATEZOLIZMAB, Solution concentrate for I.V. infusion 1200 mg in 20 mL, Tecentriq[®], Roche Products Pty Ltd

1 Purpose of Application

- 1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy Program), Authority Required (STREAMLINED) listing for atezolizumab for the treatment of previously untreated patients with extensive stage (ES) small cell lung cancer (SCLC) and Eastern Cooperative Oncology Group (ECOG) 0-1. Atezolizumab is intended to be used in combination with carboplatin and etoposide (CE) initially, then as monotherapy for maintenance.
- 1.2 The requested basis for listing was cost-effectiveness compared with CE only (placebo + CE). The key components of the clinical issue addressed by the submission are presented in Table 1.

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

Component	Description
Population	Patients with previously untreated extensive stage small cell lung cancer (ES-SCLC)
Intervention	Atezolizumab (Tecentriq [®]) in combination with carboplatin and etoposide, followed by atezolizumab monotherapy (Atezo+CE)
Comparator	Carboplatin and etoposide (CE)
Outcomes	<ul style="list-style-type: none"> • Overall survival • Progression-free survival • Safety • Quality of life, as measured by EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L
Clinical claim	In patients with previously untreated ES-SCLC, Atezo+CE is more effective than CE alone in prolonging overall survival and progression-free survival. Atezo+CE is thus superior in effectiveness and no worse in safety compared with CE. The PSCR revised the safety claim to be inferior safety versus CE alone, but that the adverse events were likely to be manageable.

Source: Table 1.1.1, p4, Section 1 of the submission.

Abbreviations: Atezo+CE=atezolizumab + carboplatin and etoposide; CE=carboplatin and etoposide; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=EuroQol 5 Dimensions 5-Level version; ES-SCLC=extensive-stage small cell lung cancer; PSCR=Pre-Sub-Committee Response; QLQ-C30=Quality-of-Life Questionnaire Core 30; QLQ-LC13=Quality-of-Life Questionnaire Lung Cancer Module.

2 Requested listing

- 2.1 The restriction requested by the submission is outlined below. Suggestions and additions proposed by the Secretariat to the requested listing are added in *italics* and suggested deletions are crossed out with ~~strikethrough~~. Changes proposed by the PBAC are added in **bold text**.

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Name, Restriction, Manner of administration and form	Max Amt	No. of Rpts	Dispensed Price for Max Amt	Proprietary Name and Manufacturer
ATEZOLIZUMAB Solution for IV infusion 1,200 mg in 20 mL vial	1,200 mg	3	Public Published:\$7560.74 Effective:\$ [REDACTED] Private Published:\$7704.63 Effective:\$ [REDACTED]	TECENTRIQ® Roche Products Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy <i>Private Hospital/Private Clinic Authority Required</i> <i>Public Hospital Authority Required</i>
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
Episodicity:	Previously untreated
Severity:	Extensive-stage <i>primary</i>
Condition:	Small cell carcinoma of lung cancer
PBS Indication:	Previously untreated extensive-stage <i>primary</i> small cell carcinoma of lung cancer
Treatment phase:	Initial treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined
Treatment Clinical criteria:	Patient must have extensive-stage small cell lung cancer, AND The condition must be previously untreated, AND Patient must have an Eastern Cooperative Oncology Group (ECOG) WHO performance status of 4 or less 0 or 1, AND The treatment must be in combination with carboplatin or cisplatin and etoposide
Administrative advice	<i>No increase in the maximum quantity or number of units may be authorised.</i> <i>No increase in the maximum number of repeats may be authorised.</i> <i>Special Pricing Arrangements apply.</i>

Name, Restriction, Manner of administration and form	Max Amt	No. of Rpts	Dispensed Price for Max Amt	Proprietary Name and Manufacturer
ATEZOLIZUMAB Solution for IV infusion 1,200 mg in 20 mL vial	1,200 mg	4	Public Published:\$7560.74 Effective:\$ [REDACTED] Private Published:\$7704.63 Effective:\$ [REDACTED]	TECENTRIQ® Roche Products Pty Ltd

Category /Program	Section 100 – Efficient funding of Chemotherapy <i>Private Hospital/Private Clinic Authority Required</i> <i>Public Hospital Authority Required</i>
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
Episodicity:	Previously untreated
Severity:	Extensive-stage <i>primary</i>

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Condition:	Small cell <i>carcinoma of lung cancer</i>
PBS Indication:	Previously untreated extensive-stage <i>primary small cell carcinoma of lung cancer</i>
Treatment phase:	Continuing treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined
Treatment Clinical criteria:	<p>The treatment must be as monotherapy, AND Patient must have previously been issued with an authority prescription for this drug for this condition, AND Patient must have stable or responding disease. Patient must not have developed disease progression while being treated with this drug for this condition</p>
Administrative advice	<p>No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>

Category/Program:	Section 100 – Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required Public Hospital Authority Required
Episodicity:	Previously untreated
Severity:	Extensive-stage <i>primary</i>
Condition:	Small cell <i>carcinoma of lung cancer</i>
PBS Indication:	Previously untreated extensive-stage <i>primary small cell carcinoma of lung cancer</i>
Treatment phase:	Grandfathering treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined
Treatment Clinical criteria:	<p>Patient must have received treatment with this drug for this condition prior to the [PBS listing date], AND Patient must have stable or responding disease. Patient must not have developed disease progression while being treated with this drug for this condition AND Patient must have had a WHO performance status of 0 or 1 prior to initiating non-PBS-subsidised treatment,</p>
Administrative advice	<p>No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>

2.2 The requested restriction is likely reasonable and consistent with the IMpower 133 trial (the primary evidence base for the submission), with the exception of the continuation criteria. In IMpower 133, patients were discontinued if they experienced “symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results if available, and the patient’s clinical status” whereas under the restriction proposed in

the submission, patients may continue even if there was disease progression as long as they were considered to be ‘responding’. The PBAC recalled that it had previously considered the continuing restriction for PD-L1s should state “Patient must not have developed disease progression while being treated with this drug for this condition” (Section 6.4, Nivolumab and ipilimumab November 2018 PSD), and considered that this same requirement should be included in the atezolizumab restriction.

- 2.3 The submission noted the standard first-line treatment regimen for ES-SCLC is chemotherapy with a platinum-based agent (either carboplatin or cisplatin) in combination with etoposide. The draft PI stated that atezolizumab is to be used in combination with carboplatin and etoposide; this was proposed as a clinical criterion in the initial restriction. The ESC considered that cisplatin did not need to be included as an alternative platinum based chemotherapy in the initial restriction as this is not commonly used in clinical practice. However, the PBAC considered that cisplatin should also be included as an alternative platinum based chemotherapy in the initial restriction as this will allow patients on either chemotherapy to access atezolizumab.
- 2.4 The submission requested a listing for initiation in patients with an Eastern Cooperative Oncology Group (ECOG) of 1 or less. The DUSC and ESC commented that it is common for patients with an ECOG performance status greater than 1 to improve to ECOG 1 or less during treatment with chemotherapy. The DUSC and ESC noted that whilst these patients were not included in the clinical trial population, provided that their ECOG improves to 1 or less during chemotherapy, treatment with atezolizumab is reasonable. The DUSC and ESC also considered there is a risk of use outside the PBS restriction in patients with ECOG performance status greater than 1. The PBAC considered that the PBS restriction for initial treatment should require patients to have an ECOG performance score of 1 or less.
- 2.5 The submission requested an Authority Required (STREAMLINED) listing to allow patients faster access to the medicine due to the aggressive nature of ES-SCLC. The submission also noted that a STREAMLINED listing is also consistent with the PBS restrictions for cancer immunotherapies such as atezolizumab in second-line NSCLC, pembrolizumab and nivolumab. The PBAC considered this to be appropriate.
- 2.6 The evaluator stated that it may be inappropriate to include a grandfathering restriction, considering the patient access program had not begun (submission claims enrolment will begin November 2019). The PBAC noted that grandfathered patients were included in the financial estimates.
- 2.7 The submission proposed that a special pricing arrangement (SPA), comprising a ■% rebate on the published price. The proposed effective Dispensed Price for Maximum Amount (DPMA) for atezolizumab 1,200 mg vial was \$ ■ with a published DPMA of \$ ■ for Public Hospital use, and \$ ■ with a published DPMA of \$ ■ for Private Hospital use.

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

3 Background

Registration status

- 3.1 The submission was made under TGA/PBAC Parallel Process. The submission stated that TGA approval is expected in November 2019. At the time of evaluation for PBAC consideration, the TGA Delegate's Overview was available. The proposed indication being considered by the TGA is atezolizumab, in combination with carboplatin and etoposide, for the first line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC). This aligns with the requested indication for this submission.
- 3.2 Atezolizumab is currently PBS listed for locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed after platinum based chemotherapy with WHO performance status 0-1.

Previous PBAC consideration

- 3.3 This is the first submission to the PBAC for atezolizumab in the treatment of ES-SCLC.

4 Population and disease

- 4.1 Lung cancer is one of the most common types of cancer in Australia, and can be generally classified as either NSCLC or SCLC based on histology and behaviour. SCLC is a highly aggressive neuroendocrine tumour, primarily affecting current and former cigarette smoking adults over 65 years of age.
- 4.2 SCLC has a negative impact on health related quality of life (HRQoL) and is associated with high mortality. SCLC can be further classified into limited stage (LS) and ES. Physically, SCLC features very fast-growing tumours with a high mitotic rate that often leads to the early development of metastatic disease. As such, it is estimated that two thirds of SCLC are diagnosed as ES-SCLC at presentation. Prognosis of SCLC without treatment is poor; with treatment median survival for patients with LS SCLC is 15 to 20 months, with 20% to 40% of patients surviving to 2 years; and in ES-SCLC, the median survival for patients is 8 to 13 months, with 5% alive at 2 years¹.
- 4.3 Atezolizumab is intended to be used alongside CE initially in first-line therapy in patients with ES-SCLC who were previously untreated and have ECOG 0-1, then used as monotherapy maintenance after four cycles of chemotherapy. The ESC and PBAC considered that the clinical management algorithm presented in the submission was appropriate and consistent with Australian clinical practice and aligns with current international lung cancer guidelines.

¹ Kelly, K 2019, 'Extensive-stage small cell lung cancer: Initial management', UpToDate, <https://www.uptodate.com/contents/extensive-stage-small-cell-lung-cancer-initial-management>

- 4.4 The ESC noted that there is a clinical need for effective treatments in SCLC given the poor prognosis and that there have been no new developments in the treatment of SCLC in 20 years.

5 Comparator

- 5.1 The submission nominated platinum based chemotherapy (cisplatin or carboplatin) + etoposide (+ placebo) as the comparator. The ESC agreed with the nominated comparator and noted that patients in the IMpower 133 trial were treated exclusively with carboplatin + etoposide, and further noted that cisplatin + etoposide is rarely used in clinical practice. The PBAC accepted the nominated comparator in the submission.

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 health care professionals (9) and organisations (2) via the Consumer Comments facility on the PBS website.
- 6.3 The comments from health care professionals described the lack of new therapies for SCLC over the last 20 years and that atezolizumab is the first drug to show improvements in survival. The comments outlined that metastatic SCLC has substantial unmet treatment needs, and that while the increase in survival with atezolizumab is small, it is a significant development for this group of patients who have a poor prognosis. The comments stated that the treatment is well tolerated.
- 6.4 The PBAC noted the support for PBS listing of atezolizumab received from the Lung Foundation of Australia. The PBAC noted the advice that, in agreement with health care professionals, the use of atezolizumab represents the first major advancement in improving survival for patients with SCLC in the last 20 years. The Lung Foundation of Australia noted the results of the IMpower 133 trial in which the addition of atezolizumab to standard chemotherapy demonstrated improved overall survival (OS) and progression free survival (PFS) without adding significant toxicity over standard chemotherapy alone.
- 6.5 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the atezolizumab in ES-SCLC submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the IMpower 133 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for atezolizumab + CE in ES-SCLC, which was

limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)², based on a comparison with CE only.

Clinical trials

6.6 The submission was based on one head-to-head randomised trial (IMpower 133; N=403) comparing atezolizumab + CE (followed by atezolizumab monotherapy) and placebo + CE (or CE only). The IMpower 133 trial is a Phase I/III, double-blind, multi-centre, placebo-controlled study of CE with or without atezolizumab in patients with untreated ES-SCLC.

6.7 Details of the trial presented in the submission are provided in Table 2.

Table 2: The trial and associated reports presented in the submission

Protocol title/ Publication title	Publication citation
Primary CSR Study GO30081, (IMpower 133). A Phase I/III, randomized, double-blind, placebo-controlled study of carboplatin plus etoposide with or without atezolizumab (anti-PD-L1 antibody) in patients with untreated extensive-stage small cell lung cancer. Report No. 1084268 (clinical cutoff 24 April 2018).	September 2018
Horn L, Mansfield AS, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer.	New England Journal of Medicine. 2018;379(23):2220-29.
Liu S, Mansfield A, Szczesna A, et al. IMpower 133: Primary PFS, OS and Safety in a PH1/3 Study of 1L Atezolizumab + Carboplatin + Etoposide in Extensive-Stage SCLC. Journal of thoracic oncology	IASLC 19th world conference on lung cancer. Canada. 2018;13(10):S185-S86.
Reck M, Mansfield AS, Liu SV, et al. IMpower 133: Phase I/III trial of first-line atezolizumab with carboplatin and etoposide in ES-SCLC.	Annals of Oncology. 2017;28:iii19.
Liu S, Reck M, Mok T, et al. IMpower 133: A phase I/III study of 1L atezolizumab with carboplatin and etoposide in patients with extensive-stage SCLC.	Journal of Thoracic Oncology. 2017;12(1):S1299.
Horn L, Mansfield AS, Reck M, et al. Phase I/III trial of atezolizumab with carboplatin and etoposide in ES-SCLC in first-line setting (IMpower 133).	Journal of Clinical Oncology. 2017;35(15).
Mok TSK, Horn L, Reck M, et al. IMpower 133: A phase I/III study of atezolizumab (atezo) with carboplatin (carbo) and etoposide as 1L therapy in patients (pts) with extensive-stage SCLC (ES-SCLC).	Annals of Oncology. 2016;27:ix169.
Horn L, Reck M, Mok TSK, et al. A Phase III study of atezolizumab with carboplatin plus etoposide in patients with extensive-stage small cell lung cancer (IMpower 133).	Annals of Oncology. 2016;27.
Horn L, Reck M, Mok T, et al. PS01.57: IMpower 133: a Phase I/III Study of 1L Atezolizumab with Carboplatin and Etoposide in Patients with Extensive-Stage SCLC:	Medical Oncology. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2016;11(11s):S305-s06.

Source: Table 2.2.1, p9-10 of Section 2 of the submission.

² Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017.

6.8 The key features of the IMpower 133 trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Atezolizumab + CE vs CE only						
IMpower 133	403	R, DB 13.9 mths	Low	Untreated ES-SCLC ECOG 0-1	OS, PFS, HRQoL	Used OS, HRQoL (by proximity to death), TTTD

R=randomised; DB=double blind; ECOG=Eastern Cooperative Oncology Group; ES-SCLC=extensive stage small cell lung cancer; OS=overall survival; PFS=progression-free survival; HRQoL=health related quality of life, TTTD=time to treatment discontinuation.
Source: Constructed during evaluation.

6.9 IMpower 133 is an ongoing trial that enrolled 403 patients with ES-SCLC and ECOG 0-1 who were previously untreated for ES-SCLC. Patients were randomised to receive treatment with atezolizumab + CE for four cycles then atezolizumab as monotherapy maintenance (n=202, median duration of treatment including initiation=4.7 months), or CE + placebo for four cycles then placebo as monotherapy (n=201, median duration of treatment including initiation=4.1 months).

6.10 The main inclusion criteria were adults aged 18 years or older who had ES-SCLC, ECOG 0-1 who had not received prior treatment for ES-SCLC. The trial excluded patients who had notable comorbidities (long list of conditions including, but not limited to, cardiovascular disease, active central nervous system metastases, autoimmune disease) or who had received immune system related treatments (e.g. vaccinations and immunotherapy or suppressants). The inclusion criteria in IMpower 133 were consistent with the proposed PBS indication. However, the extensive exclusion criteria in IMpower 133 for comorbidities may indicate that the population of IMpower 133 might be narrower than the proposed population, though the impact of this is unclear.

6.11 Interim OS results (median follow up 13.9 months, data cut off 24 April 2018) of IMpower 133 were presented in the submission. The Pre-Sub-Committee Response (PSCR) and pre-PBAC response provided updated OS results from a January 2019 data-cut, which provided an additional 9 months of follow-up data. The PSCR stated that no further formal OS analyses of IMpower 133 are planned.

Comparative effectiveness

6.12 The OS results of patients in IMpower 133 are presented in Tables 4 and 5 and in Figures 1 and 2. Updated data from the January 2019 data-cut have been included where available. An updated Kaplan-Meier curve was provided by the sponsor in the pre-PBAC response.

Table 4: Overall survival in the ITT population in IMpower 133 (interim cutoff April 2018 and January 2019)

Efficacy parameter	Atezo+CE (N=201)	PBO+CE (N=202)
April 2018 data-cut (provided in submission)		
Patients with event, n (%)	104 (51.7)	134 (66.3)
Time to event (months)		
Median (95% CI)	12.3 (10.8, 15.9)	10.3 (9.3, 11.3)
25% and 75% percentile	7.4, 17.8	7.1, 15.8
Range	0.0*, 21.1*	0.0*, 21.4*
Hazard ratio (95% CI)	0.701 (0.541, 0.909)	
P-value	0.0069^a	
January 2019 data-cut (provided in PSCR)		
Hazard ratio (95% CI)	0.755 (0.601, 0.949)	
P-value	0.0154 ^b	

Text in bold indicate statistically significant differences.

* Censored.

^a Interim Analysis OS data from April 2018 cutoff was tested at two-sided alpha of 0.0193 (with 238 observed OS events) to control the overall two-sided type I error for OS at 0.045 by Lan DeMets function approximating O'Brien-Fleming boundary. (Note that IMpower 133 was designed around an overall two-sided type I error rate at 0.05, and using a group sequential weighted Holm procedure, a two sided significance level of 0.045 and 0.005 were assigned to OS and PFS, respectively. The CSR provided with the PSCR also notes that 'the two interim and final analyses of OS use the Lan-DeMets alpha spending function to approximate the O'Brien-Fleming boundary' though it is unclear whether two interim analyses were initially planned, or if the two analyses referred to the interim and final analyses.)

^b The p-value required for statistical significance was not stated in PSCR. The p-value was described as for 'descriptive purposes only' in the updated CSR for IMpower 133, provided with the Pre-PBAC response.

Atezo+CE=atezolizumab + carboplatin and etoposide; PBO+CE=placebo + carboplatin and etoposide; CI=confidence interval; ITT=intention to treat; PSCR=pre-sub-committee response.

Source: April 2018 data-cut: Table 2.5.1, p23, Section 2 of the submission, Table 18 of CSR; January 2019 data-cut: Table 4 of updated CSR provided with the Pre-PBAC response.

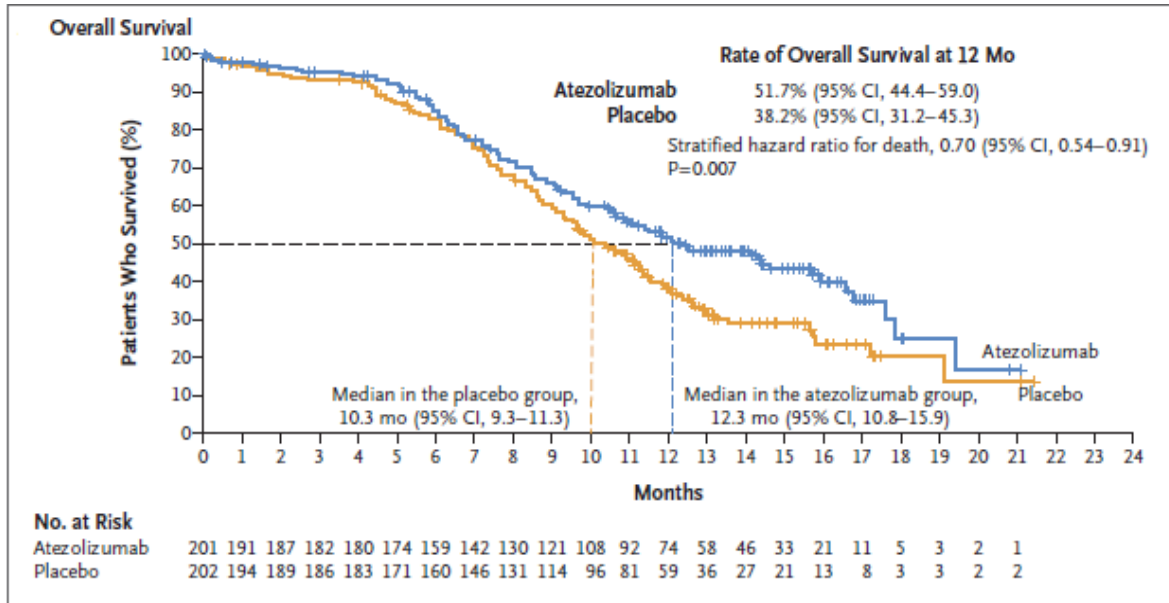
Table 5: OS in the ITT population in IMpower 133 at specific time-points (interim cutoff April 2018 and January 2019)

Months	Interim analysis: April 2018 Event rate, % (95% CI)			OS update: January 2019 Event rate, % (no 95% CIs provided)		
	Atezo+CE	PBO+CE	Difference	Atezo+CE	PBO+CE	Difference
6 months	85.8% (80.8, 90.8)	82.8% (77.5, 88.0)	3.1% (-4.2, 10.3)	85.8%	82.8%	3.0%
12 months	51.7% (44.4, 59.0)	38.2% (31.2, 45.3)	13.5% (3.3, 23.6)	51.9%	39.0%	12.9%
18 months	25.0% (11.2, 38.7)	20.2% (11.1, 29.4)	4.7% (-11.8, 21.2)	34.0%	21.0%	13.0%

CI = confidence interval, ITT = intention to treat

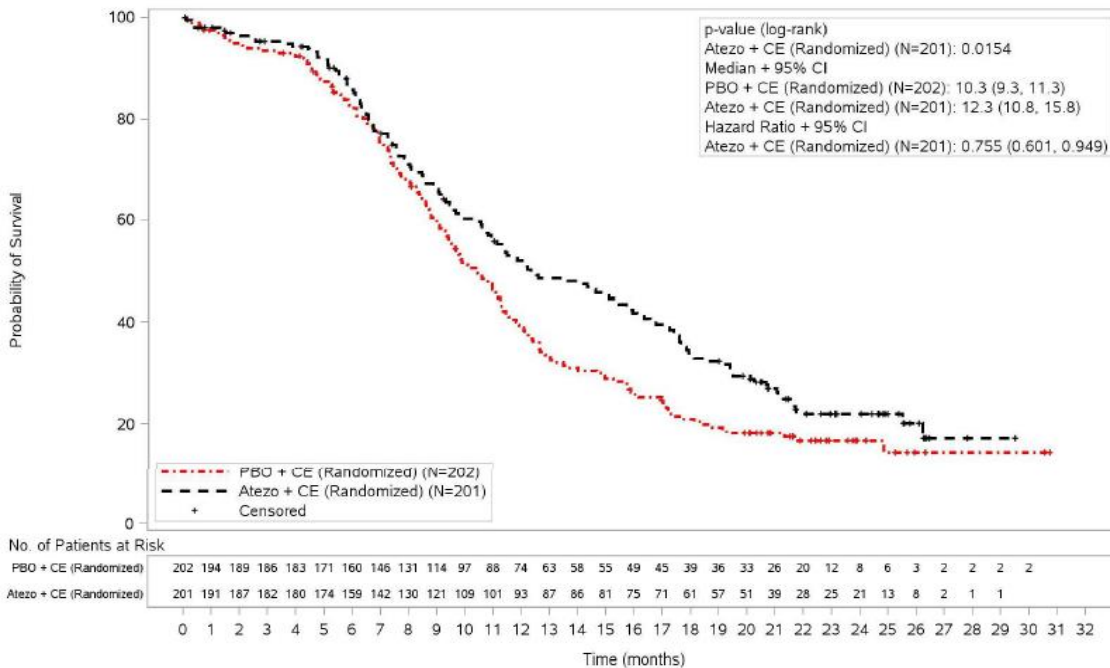
Source: Table 1, PSCR; Table 2.5.1, p23, Section 2 of the submission; April 2018 data-cut: Table 18 of CSR and pp 601-602 of CSR; January 2019 data-cut: p28-29 of updated CSR provided with the Pre-PBAC response.

Figure 1: Overall survival in IMpower 133 (interim cutoff April 2018)



Source: Figure A, p6 Horn 2018.

Figure 2: Overall survival in IMpower 133 (data cutoff January 2019)



Source: Figure 2, p21 of updated CSR provided with the Pre-PBAC response.

6.13 IMpower 133 demonstrated a modest (2.0 months median increase), but statistically significant improvement in OS for patients treated with atezolizumab + CE compared to patients treated with placebo + CE. In the April 2018 data-cut, the hazard ratio for OS was 0.70 (95% CI: 0.54, 0.91), p=0.007. This met the pre-specified significance threshold for the interim analysis (which required p=0.0193 for significance, in place

because of multiple testing considerations). In the updated January 2019 data-cut, the hazard ratio for OS was 0.755 (95% CI: 0.601, 0.949), $p=0.0154$. The PSCR stated that the updated data demonstrated a 13% improvement in 18 month OS in favour of atezolizumab + CE.

- 6.14 The median OS in patients treated with placebo + CE in IMpower 133 appears to be in line with previous studies (e.g. a review by Brahmer and Ettinger in 1998 reported a median time to survival for ES-SCLC patients treated with CE of between 4.6 and 12 months).
- 6.15 The ESC noted that the PSCR only provided an updated hazard ratio for OS and survival rates at three specific time-points from the January 2019 cutoff, and considered further information would be required to clarify the survival gains. In particular, the ESC noted that updated Kaplan-Meier curves, time on treatment information and data on subgroup results for patients under and over 65 years would be useful to consider, and the median duration of follow-up in the new data-cut was unclear. The pre-PBAC response provided further information from the January 2019 cutoff, including the updated Kaplan-Meier curve provided above, and updated data on the subgroup results for patients under and over 65 years (refer to Paragraph 6.23).
- 6.16 The submission claimed that the benefit in OS was considered a grade 4 benefit (out of 5) on the ESMO-MCBS indicating a 'high level of proven clinical benefit'. This conclusion relies on acceptance that there is a benefit in patient quality of life (QoL) (discussed further in Paragraphs 6.19 to 6.21), which improves the ESMO-MCBS grade for IMpower 133 from 3 to 4. The MOGA noted that although there is a suggestion of improvement in QoL in IMpower 133, it is unclear if there is a statistically significant difference in global QoL. Therefore, the ESMO-MCBS score was not upgraded to a 4.
- 6.17 The results for PFS from the April 2018 data-cut of IMpower 133 are presented in Table 6 and Figure 3. The CSR stated this was the final analysis of PFS (as such, no further PFS results were provided from the January 2019 cutoff).

Table 6: Progression-free survival in the ITT population in IMpower 133 (April 2018 data-cut, final analysis of PFS)

Efficacy parameter	Atezo+CE (N=201)	PBO+CE (N=202)
Patients with event, n (%)	171 (85.1)	189 (93.6)
Earliest contributing event, n (%)		
Death	19 (9.5)	20 (9.9)
Disease progression	152 (75.6)	169 (83.4)
Time to event (months)		
Median (95% CI)	5.2 (4.4, 5.6)	4.3 (4.2, 4.5)
25% and 75% percentile	4.1, 7.2	4.0, 5.7
Range	0.0*, 21.1	0.0*, 17.3 [^]
Hazard ratio (95% CI)	0.772 (0.624, 0.955)	
P-value	0.0170^a	
6-month time point analysis		
Patients remaining at risk	58	44
Event-free rate (95% CI)	30.86 (24.26, 37.45)	22.39 (16.56, 28.22)
Difference in event-free rate (95% CI)	8.47 (-0.33, 17.27)	
12-month time point analysis		
Patients remaining at risk	21	9
Event-free rate (95% CI)	12.62 (7.85, 17.40)	5.35 (2.14, 8.56)
Difference in event-free rate (95% CI)	7.27 (1.52, 13.02)	

Text in bold indicate statistically significant differences.

* = censored

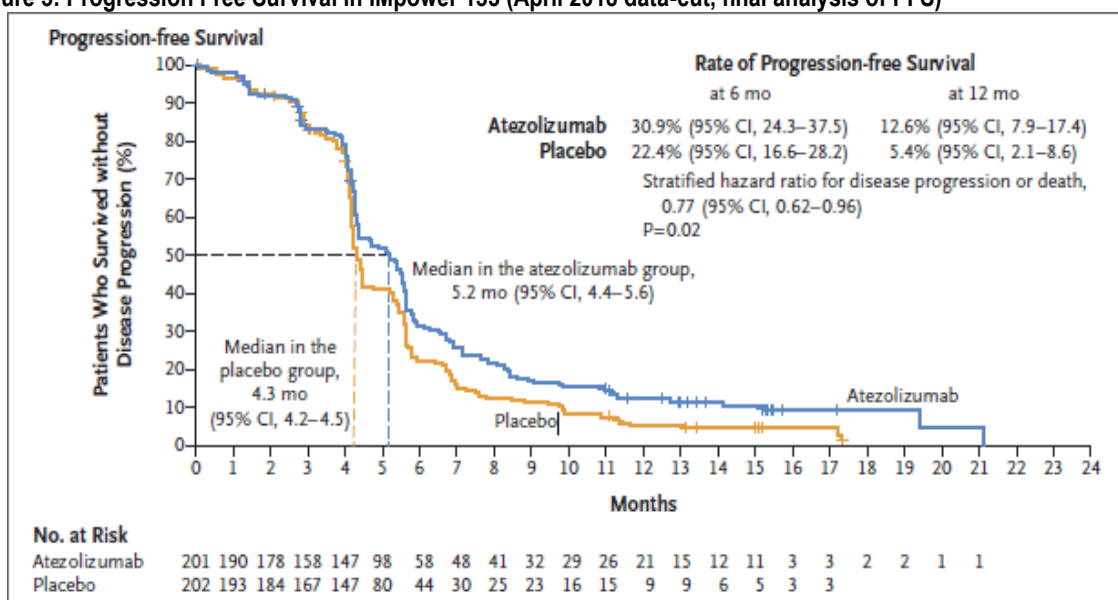
[^] = censored and event

^a Since null hypothesis for OS was rejected at an overall two-sided significance level of 0.045, PFS was tested at two-sided type I error of 0.05.

CI=confidence interval, ITT=intention to treat.

Source: Table 2.5.2, p25 of Section 2 of the submission, Table 19 of CSR.

Figure 3: Progression Free Survival in IMpower 133 (April 2018 data-cut, final analysis of PFS)



Source: Figure B, p6 Hom 2018.

- 6.18 As for OS, IMpower 133 demonstrated a modest, but statistically significant improvement in PFS for patients treated with atezolizumab + CE compared to patients treated with placebo + CE. The evaluation considered that it was unclear if the magnitude of difference in PFS (0.9 months median increase) between atezolizumab + CE and placebo + CE is clinically meaningful. It should also be noted that PFS had minimal impact on the economic model presented by the submission. The ESC accepted this modest improvement in PFS but noted that PFS may not be an appropriate assessment of benefit for immunotherapies (due to pseudo-progression). The PBAC considered it was unclear if the magnitude of difference in PFS (0.9 months median increase) between atezolizumab + CE and placebo + CE was clinically meaningful.
- 6.19 IMpower 133 included patient reported quality of life outcomes based on the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLC-LC13 questionnaires. However, no statistical tests were conducted around these results, therefore it is unclear if the differences (assuming there were any) in the subscales in the questionnaires observed in IMpower 133 were clinically meaningful.
- 6.20 While EuroQol 5 Dimensions 5-Level version (EQ-5D-5L) results were collected as part of IMpower 133, only a summary of the results by progression status and time to death were presented in the submission as part of economic evaluation. There was insufficient information presented in the EQ-5D results for meaningful analysis.
- 6.21 The submission (p31) claimed that patients receiving atezolizumab + CE experienced clinically meaningful improvements (i.e. ≥ 10 point score decrease from baseline) in cough, chest pain, and dyspnoea earlier, and generally reported more enduring improvements than those in the placebo + CE arm. This claim was not supported as:
- None of the hazard ratios (HRs) were statistically significantly different for cough (HR=1.221, 95% CI: 0.795, 1.874), pain in chest (HR=1.058, 95% CI: 0.722, 1.553) or dyspnoea (HR=0.748, 95% CI: 0.549, 1.019) between treatment arms;
 - While the Kaplan Meier curves for time to deterioration in cough, pain in chest and dyspnoea were presented, it was unclear what direction or magnitude of difference between treatments would indicate a clinically meaningful worsening of symptoms and which treatment arm has a numerically superior profile. Regardless, the trends for cough, pain in chest and dyspnoea were not consistent. Cough and pain in chest favours one treatment whereas dyspnoea favours the other treatment; and
 - The differences in the point estimates for ‘mean change from baseline at end of treatment’ between patients treated with atezolizumab + CE and placebo + CE in cough, pain in chest and dyspnoea were small (all < 6.5 points) and did not meet the “ > 10 point change” criteria proposed by the submission.
- 6.22 Overall, IMpower 133 demonstrated that there was a statistically and clinically significant benefit in OS in patients treated with atezolizumab + CE compared to CE only, but has not sufficiently demonstrated that ES-SCLC patients treated with atezolizumab + CE had improved health related quality of life (HRQoL) compared to

patients treated with placebo + CE. Therefore, the submission's claim of an ESMO-MCBS grade of 4 may not be supported.

- 6.23 A pre-specified subgroup analysis (from the April 2018 data-cut) showed that treatment with atezolizumab + CE resulted in statistically significantly improved OS compared to placebo + CE in patients who were aged 65 or more (HR=0.53, 95% CI: 0.36, 0.77; n=186), but not in patients aged less than 65 years (HR=0.92, 95% CI: 0.64, 1.32; n=217). The test of interaction between patients aged less than 65 years was also statistically significant (p=0.0395) indicating that patient age was a treatment effect modifier. The discrepancy in the two subgroups was driven by longer OS in patients treated with placebo + CE in patients aged <65 years (10.9 months) compared to patients aged ≥65 years (9.5 months) while the OS in patients treated with atezolizumab + CE was reasonably consistent across the two subgroups (12.3 and 12.5 months in patients aged <65 and ≥65 years, respectively). The PSCR argued that the pre-specified subgroups were “not adequately powered to detect a statistically significant difference in treatment” and that subgroup analyses are “not relevant”. However, the ESC disagreed and considered the subgroup was adequately powered as a difference had been detected and noted that each of these two groups made up half of the trial population. The ESC also noted the PBAC has previously expressed concerns regarding subgroup interactions for age in nivolumab for NSCLC (nivolumab for NSCLC PSD, March 2017). However, the ESC also acknowledged that there was a possibility that the result was a false positive given the number of subgroups analysed and no statistical adjustment for multiple comparisons (for the subgroups) appeared to have been made. The pre-PBAC response provided updated data from the January 2019 data-cut for this subgroup; the results were consistent with the April 2018 data-cut.

Comparative harms

- 6.24 A summary of the incidence of the adverse events (AEs) that were statistically significantly different between treatment groups in IMpower 133 (April 2018 data-cut) are presented in Table 7.

Table 7: Overview of adverse events and deaths in the safety population in IMpower 133 (April 2018 data-cut)

Adverse event	Atezo+CE (N=198) ¹		Placebo+CE (N=196) ¹		Atezolizumab+CE vs. placebo+CE	
	n	%	n	%	RR (95% CI)	OR (95% CI)
Any AE	198	(100.0)	189	(96.4)	1.04 (1.01, 1.07)	15.71 (0.92, 330.39)
Treatment-related AE	188	(94.9)	181	(92.3)	1.03 (0.98, 1.08)	1.56 (0.64, 3.98)
Atezolizumab/placebo	128	(64.6)	98	(50.0)	1.29 (1.09, 1.54)	1.83 (1.20, 2.80)
AE leading to withdrawal	22	(11.1)	6	(3.1)	3.63 (1.50, 8.76)	3.96 (1.51, 12.18)
Atezolizumab/placebo	21	(10.6)	5	(2.6)	4.16 (1.60, 10.81)	4.53 (1.61, 15.66)
Number of patients with at least one:						
AESI	79	(39.9)	48	(24.5)	1.63 (1.21, 2.20)	2.05 (1.30, 3.23)
Treatment related AESI	64	(32.3)	36	(18.4)	1.76 (1.23, 2.52)	2.12 (1.30, 3.50)
Grade 3-4 AESI	16	(8.1)	5	(2.6)	3.17 (1.18, 8.48)	3.36 (1.14, 11.93)
Treatment related grade 3-4 AESI	14	(7.1)	4	(2.0)	3.46 (1.16, 10.34)	3.65 (1.12, 15.47)
Specific Treatment related AEs which were statistically significantly different between treatment groups						
Decreased appetite	41	(20.7)	26	(13.3)	1.56 (1.00, 2.45)	1.71 (0.97, 3.05)
Immune-related rash	37	(18.7)	20	(10.2)	1.83 (1.10, 3.04)	2.02 (1.09, 3.83)
Immune-related hypothyroidism	25	(12.6)	1	(0.5)	24.75 (3.39, 180.87)	28.18 (4.49, 1162)

Source: Table 2.5.8, p32, Table 2.5.12, p36 and Table 2.5.16, p40, Section 2 of the submission

¹Mean exposure to atezolizumab + CE was 5.7 months and to placebo + CE was 5.0 months (Table 2.5.9, p34, Section 2 of the submission)
Notes: Relative risks and 95% confidence intervals for relative risks were calculated using the Normal approximation to the binomial distribution.

Text in bold indicate statistically significant results. Text in italics indicate values calculated during evaluation using StatsDirect 3.1.22 using random effects

Abbreviations: AE=adverse event; CI=confidence interval, AESI = adverse event of special interest

6.25 Adverse events of special interest (AESI) include:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, or adrenal insufficiency or hyperthyroidism
- Hepatitis
- Transaminitis: Grade ≥ 2 (AST or ALT $> 3 \times$ upper limit of normal (ULN) and bilirubin $> 2 \times$ ULN) OR AST/ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurologic: Guillain-Barré syndrome, myasthenia gravis, meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity
- Cases of potential drug induced liver injury
- Suspected transmission of an infectious agent by the study drug

6.26 The commentary noted that atezolizumab was associated with a statistically significantly higher rate of decreased appetite, immune-related rash and immune-related hypothyroidism. The PSCR revised the safety claim to be that “atezolizumab + CE was inferior to placebo + CE in terms of safety, but the AEs were likely to be manageable”.

- 6.27 As a relatively new drug, which is still undergoing clinical trials for other yet to be approved conditions, new safety signals are continually detected and investigated. The latest Periodic Benefit-Risk Evaluation Report (PBRER) added three new AEs with atezolizumab monotherapy (oropharyngeal pain, nasopharyngitis, hyperglycaemia) and eight new AEs from clinical trials which were not reported in monotherapy trials (dysphonia, headache, proteinuria, dysgeusia, dizziness, lung infection, syncope, lymphocyte count decreased). Additionally, three safety signals (grade 5 cardiac failure with atezolizumab and bevacizumab, histiocytosis haematophagic, and myositis) are ongoing. It is likely that the list of adverse events associated with atezolizumab treatment reported in IMpower 133 were not exhaustive, and more safety signals and adverse events will be noted and reported as more patients are treated with atezolizumab and clinical trials of atezolizumab continue.

Benefits/harms

- 6.28 A summary of the comparative benefits and harms for atezolizumab + CE versus CE only is presented in Table 8.

Table 8: Summary of comparative benefits and harms for atezolizumab + CE and CE only

Benefits						
Time-to-event outcome: IMpower 133 (median duration of follow up 13.9 months), April 2018 cutoff						
	Atezolizumab + CE	CE only	Absolute difference	HR (95% CI)		
Deaths, n/N (%)	104/201 (51.7)	134/202 (66.3)	-	0.70 (0.51, 0.91)		
% alive at 12 months (95% CI)	51.69% (44.35, 59.03)	38.23% (31.38, 45.27)	13.46% (3.29, 23.64)			
Progressed, n (%)	171/201 (85.1)	189/202 (93.6)	-	0.77 (0.62, 0.96)		
% not progressed at 12 months, (95%CI)	12.62% (7.85, 17.40)	5.35% (2.14, 8.56)	7.27% (1.52, 13.02)			
January 2019 cutoff (median duration of follow-up 22.9 months)						
% alive at 18 months	34.0%	21.0%	13.0%			
Harms (April 2018 cutoff)						
Adverse event	Atezolizumab + CE n/N	CE only n/N	RR (95% CI)	Event rate/100 patients*		RD# (95% CI)
				Atezolizumab + CE	CE only	
Any AE	198/198	189/196	1.04 (1.01, 1.07)	100	96.4	0.036 (0.016, 0.072)
Atezolizumab/placebo related AE	128/198	98/196	1.29 (1.09, 1.54)	64.6	50.0	0.147 (0.048, 0.241)
Number of patients with at least one						
Treatment related AESI	64/198	36/196	1.76 (1.23, 2.52)	32.3	18.4	0.140 (0.054, 0.224)
Treatment related grade 3-4 AESI	14/198	4/196	3.46 (1.16, 10.34)	7.1	2.0	0.050 (0.010, 0.097)
Decreased appetite	41/198	26/196	1.56 (1.00, 2.45)	20.7	13.3	0.074 (0.0001, 0.15)
Immune related rash	37/198	20/196	1.83 (1.10, 3.04)	18.7	10.2	0.085 (0.016, 0.155)
Immune related hypothyroidism	25/198	1/196	24.75 (3.4, 180.1)	12.6	0.5	0.121 (0.079, 0.175)

Median duration of follow-up in IMpower 133: Atezolizumab + CE = 13.9 months, CE only = 13.2 months

HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio; OS = overall survival; PFS = progression free survival; AE = adverse event; AESI = Adverse event of special interest

Text in bold indicate statistically significant results.

Values were calculated during evaluation using StatsDirect 3.1.22

Source: table 2.5.1, p23, Table 2.5.2, p25 and IMpower 133 CSR, pp871-945

6.29 On the basis of direct evidence presented by the submission, for every 100 patients treated with atezolizumab + CE in comparison to CE only:

- Approximately 13 additional patients will remain alive after 18 months; and
- Approximately 7 additional patients will remain progression free after 12 months.

6.30 On the basis of direct evidence presented by the submission, for every 100 patients treated with atezolizumab + CE in comparison to CE only over a median duration of follow-up 13.9 months (based on April 2018 cutoff):

- Approximately 15 additional patients would experience adverse events specifically related to atezolizumab.
- Approximately 7 additional patients would experience decreased appetite.
- Approximately 9 additional patients would experience immune related rash.
- Approximately 12 additional patients would experience immune related hypothyroidism.

Clinical claim

- 6.31 The submission described atezolizumab + CE as superior in terms of effectiveness and ‘no worse’ in terms of safety compared to carboplatin and etoposide in patients with previously untreated ES-SCLC. The commentary noted these claims were not fully supported by the evidence presented in the submission.
- 6.32 Although IMpower 133 demonstrated that patients treated with atezolizumab + CE had statistically significantly improved OS compared to patients treated with placebo + CE, the commentary noted the following also needed to be considered:
- The OS data were based on an interim analysis that showed a modest increase in OS. It was unknown whether the magnitude of the difference would remain unchanged with a longer follow-up. The PSCR and pre-PBAC response provided additional OS data from a January 2019 cutoff.
 - IMpower 133 has not sufficiently demonstrated that patient’s HRQoL was improved or that deterioration of HRQoL was delayed. None of the hazard ratios for ‘time to deterioration’ in cough (HR=1.221, 95% CI: 0.795, 1.874), pain in chest (HR=1.058, 95% CI: 0.722, 1.553) or dyspnoea (HR=0.748, 95% CI: 0.549, 1.019) were statistically significantly different between treatment groups, and there was no consistency between the three symptoms with regards to which treatment may potentially be favoured. No formal statistical tests were conducted for other HRQoL measurements. The submission’s claim of improved HRQoL (which would be required to increase the ESMO-MCBS grade from 3 to 4 to meet a criteria of ‘high level of proven clinical benefit’) was not supported by the evidence.
- 6.33 The ESC noted that the PSCR provided updated OS data from a January 2019 data-cut which reported a 13% improvement in 18 month OS in favour of atezolizumab + CE. The hazard ratio for OS, reported in the January 2019 data-cut, was 0.755 (95% CI: 0.601, 0.949), p=0.0154.
- 6.34 Overall, the ESC and PBAC considered that the OS data indicated that treatment with atezolizumab + CE resulted in a modest but clinically meaningful increase in survival when compared to placebo + CE. However, the ESC and PBAC considered that the magnitude of the OS benefit remained uncertain and the durability of the gain in survival was unclear given the relatively short duration of follow-up with the updated data-cut. The ESC and PBAC considered that ES-SCLC is an aggressive disease and patients generally deteriorate rapidly once progressive disease develops, so it was uncertain how long patients would continue to respond to treatment. The ESC noted that no further formal OS analyses of IMpower 133 are planned following the January 2019 data-cut.
- 6.35 The ESC considered that there was no evidence presented that atezolizumab would be associated with an increase in quality of life.
- 6.36 The claim of ‘no worse’ safety in the submission was also not adequately supported by the evidence presented because patients treated with atezolizumab + CE were

statistically significantly more likely to experience a range of AEs compared to patients treated with placebo + CE in IMpower 133 (see Table 7 above). The PSCR accepted the revised safety claim proposed by the commentary: that atezolizumab + CE was inferior to placebo + CE in safety, but the AEs are likely to be manageable. The PBAC and the ESC considered the update to the safety claim to be appropriate.

- 6.37 The PBAC considered that the claim of superior comparative effectiveness of atezolizumab + CE compared with CE only was reasonable with respect to OS, however the magnitude and durability of the benefit was uncertain.
- 6.38 The PBAC considered that the revised claim of inferior comparative safety with manageable AEs of atezolizumab + CE compared with CE only was reasonable.

Economic analysis

- 6.39 The submission presented a stepped economic evaluation based on direct randomised trial (IMpower 133). A summary of the model structure is presented in Table 9.

Table 9: Summary of model structure and rationale

Component	Summary
Type of analysis	Cost-utility analysis
Outcomes	Life years gained and quality-adjusted life years
Time horizon	Five years in the model base case vs. 13.9 months median follow up in the IMpower 133 trial
Methods used to generate results	Partitioned survival cohort analysis
Health states	Three: progression-free disease, progressive disease and death (both alive health states are further segregated based on whether the person is on treatment or not)
Cycle length	1 week
Transition probabilities	Health state allocation over time determined by progression-free survival and overall survival curves from IMpower 133 at the 24 April 2018 clinical cut-off
Software package	Microsoft Excel

Source: Table 3.1.1, p7 Section 3A of the submission

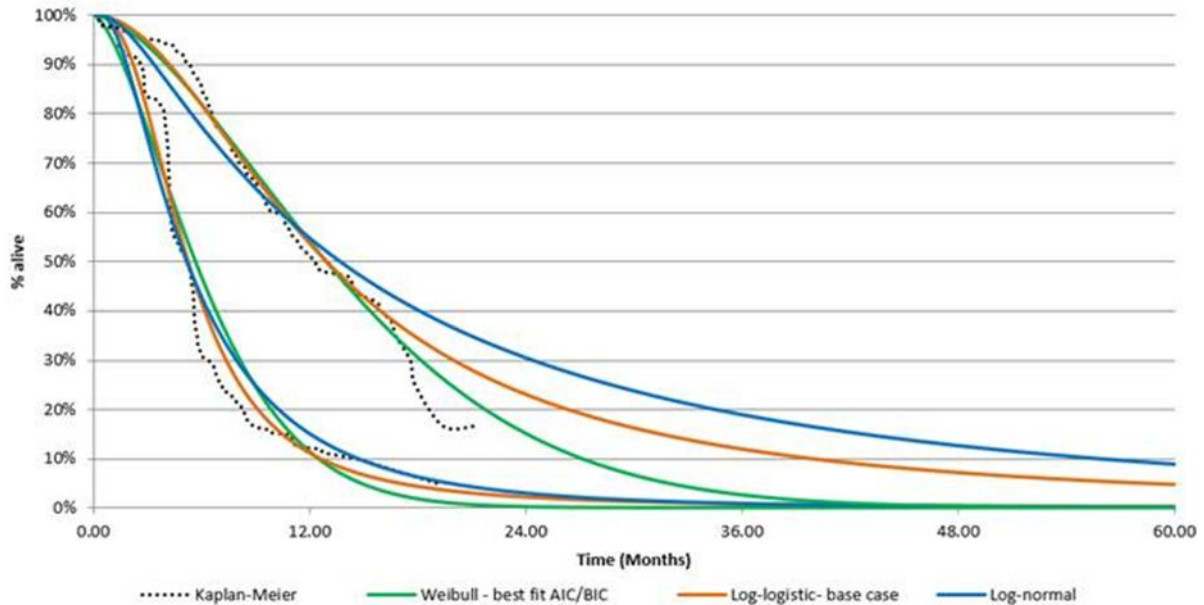
- 6.40 The submission described the model as a partitioned survival analysis with progression free, progressed and dead as three health states. This is only a partially accurate description as it does not capture the state of being ‘on treatment’ which was modelled separately in the economic model. Additionally there was no explicit link between progression and being on treatment in the model: it was possible to remain on treatment after progression in the model, which may not be consistent with the clinical trial.
- 6.41 Disease progression within the economic model had almost no impact on the overall outcome. Neither drug usage costs (which were estimated based on observed ‘time to treatment discontinuation’) nor utilities (which were estimated based on a ‘time to death’ function which was correlated to OS, but not PFS directly) was affected by whether a patient had progressive disease or not. The only cost which is affected by time spent in PFS was a medical cost for CT, which was \$560 applied every 6 weeks until progression. Therefore, assuming no difference in PFS between the two

treatments (i.e. assume PFS for atezolizumab + CE is the same as placebo + CE) results in a change in the ICER of less than █%.

- 6.42 The model used observed data from IMpower 133 for OS, PFS and time to treatment discontinuation (TTTD) up to 13.9 months, and then used a parametric function to extrapolate each of the curves to up to 5 years. No convergence of OS was assumed in the base case. The model did not include updated clinical data from the January 2019 data-cut; while the updated clinical data from the January 2019 cutoff were included in the PSCR, the model results were not updated in the Pre-PBAC response.
- 6.43 The commentary noted it may not have been appropriate for the submission to truncate all the extrapolations at median follow up in IMpower 133 (13.9 months). The commentary stated that given the vast majority (>85%) of patients had already discontinued or progressed, using the median follow up for PFS and TTTD as the truncation point may not be appropriate because of the small number of patients remaining event-free at this point, potentially resulting in unreliable results. This was tested in sensitivity analyses.
- 6.44 The OS extrapolation had a significant impact on the ICER. Extrapolation of OS is shown in Figures 4 and 5 (a comparison of the parametric functions is shown in Figure 4 and the OS estimates applied in the model are shown in Figure 5). The submission extrapolated OS using the log logistic function, despite the Weibull function having the lowest AIC/BIC. The submission stated that the log logistic function most closely resembled the survival estimates for patients with ECOG 0-1 with ES-SCLC treated with CE in a longitudinal US database (the Flatiron Health Database). However, the Flatiron Health Database was based on only a small number of patients at risk at Years 3 and 5 (15 and 1 patient/s at risk in Years 3 and 5, respectively).
- 6.45 The PSCR and pre-PBAC response argued that the log logistic extrapolation for OS in the CE only arm was appropriate and was ‘comparable’ to the observed 18 month OS in IMpower 133 from the updated January 2019 data-cut. However, the ESC noted that the data from the January 2019 data-cut were from single points in time and, in the absence of the full Kaplan-Meier curves, were difficult to compare with the model extrapolations.
- 6.46 The ESC considered that, based on the information available, the Weibull function may be an appropriate alternative for extrapolation of OS as it had the lowest AIC/BIC and resulted in a more conservative extrapolation. Using the Weibull extrapolation for OS for both treatment arms significantly increased the base case ICER to \$105,000/QALY - \$200,000/QALY (█% increase from the base case).
- 6.47 Further, the ESC considered that it may not be reasonable to assume a continued treatment effect over the duration of the time horizon as the durability of the gain in survival was unclear given the aggressive nature of ES-SCLC and the relatively short duration of follow-up (even with the updated data-cut). The ESC considered that an alternative scenario would be for the OS curves to begin to converge at 24 months

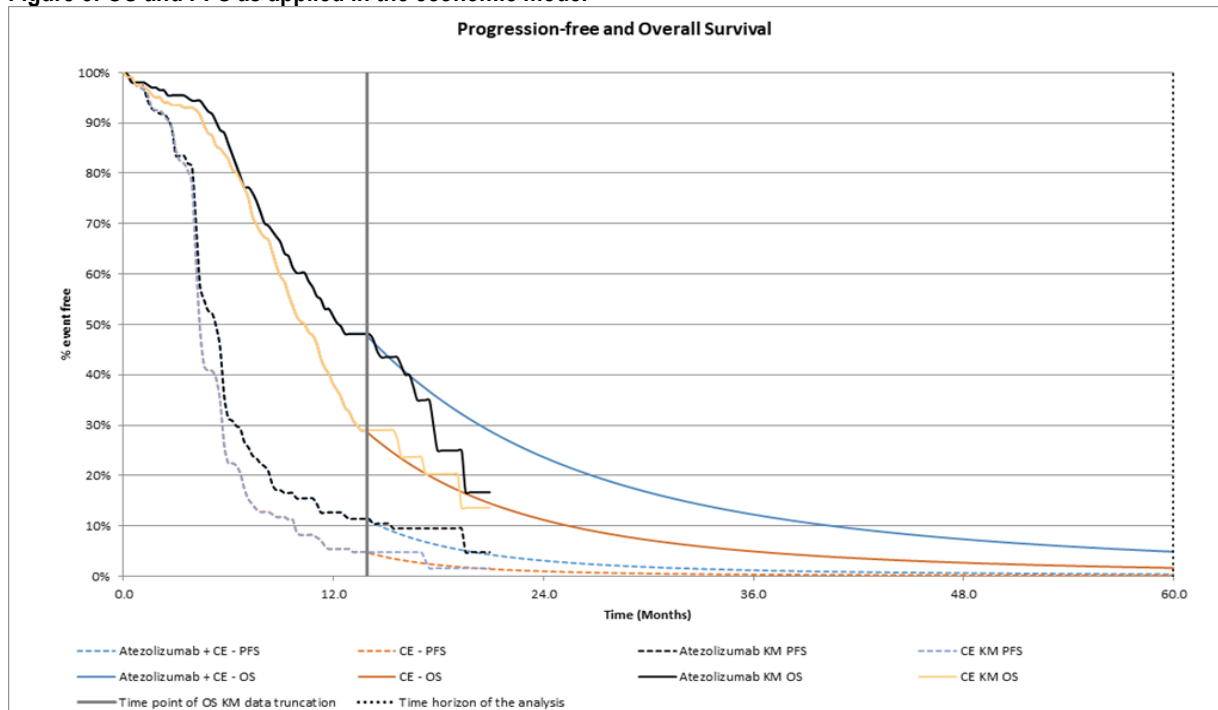
with convergence at 60 months. This increased the ICER to \$105,000/QALY - \$200,000/QALY (██████% increase from base case).

Figure 4: Comparison of parametric functions for OS data



Source: Economic Evaluation.xlsx 'Parametric Functions', only the functions discussed above are presented in the graph for simplicity.

Figure 5: OS and PFS as applied in the economic model



Source: Economic Evaluation.xlsx, worksheet 'Results tables'

6.48 The submission used four 'proximity to death' sub-states and assigned utility to each state based on EQ-5D-5L results reported by patients in IMpower 133 (Table 10). The

commentary and the ESC considered there were several issues with the proximity to death utilities presented:

- No justification for the intervals chosen was provided;
- No confidence intervals around estimates were presented, and it was unclear if there were any statistically significant differences between the nominated intervals to justify using different values at each interval. Further the number of patients at each time interval was not presented;
- There was a large difference in utilities for ‘on’ versus ‘off’ treatment for patients at similar times to death (e.g. in patients with ≤ 5 weeks to death, the ‘on treatment’ utility was [REDACTED], while the ‘off treatment’ utility was [REDACTED]). While pooled results for each time interval were used in the base case, the validity of such large differences is unclear; and
- The method to pool data was not provided. The ESC questioned the methodology as it resulted in implausible results where the pooled utility at >30 weeks ([REDACTED]) was greater than the utility for both on treatment ([REDACTED]) and off treatment ([REDACTED]), and at >10 but ≤ 30 weeks the utility for patients ‘on treatment’ was similar to the pooled utility. The ESC requested the sponsor provide clarification regarding the methodology for pooling the utilities. The pre-PBAC response confirmed the utility weights were estimated using Norman (2012) where the trial collected EQ-5D-5L data.

Table 10: Utilities based on proximity to death

Proximity to death	On treatment	Off treatment	Pooled (base case)
≤ 5 weeks	[REDACTED]	[REDACTED]	[REDACTED]
>5 but ≤ 10 weeks	[REDACTED]	[REDACTED]	[REDACTED]
>10 but ≤ 30 weeks	[REDACTED]	[REDACTED]	[REDACTED]
>30 weeks	[REDACTED]	[REDACTED]	[REDACTED]

Source: Economic Evaluation.xlsx, worksheet ‘Utilities’

6.49 The submission also provided health state utilities from IMpower 133 based on whether patients had progressed, which were used in sensitivity analyses. The progression free health state had a utility estimate of [REDACTED] and the progressed health state had a utility estimate of [REDACTED]. The ESC considered that it may not be clinically plausible for the two health states to have such similar utilities, and considered this may indicate limited availability of EQ-5D data in patients post-progression in IMpower 133 (which may also affect the reliability of the utilities based on proximity to death; as noted above the number of patients at each time interval was not presented).

6.50 The key drivers of the economic model are summarised in Table 11. Overall, most of the assumptions of time horizon, extrapolation parameters, time on treatment and utilities favoured treatment with atezolizumab.

Table 11: Key drivers of the model

Description	Method/Value	Impact																																								
Parametric function for OS extrapolation	<p>The submission used the log logistic function for OS in both treatment arms even though the Weibull function had the lowest AIC/BIC. For atezolizumab + CE the log logistic form was chosen based on expert opinion.</p> <p>The submission assumed that log logistic was the most appropriate extrapolation function for CE only, arguing that it most resembled the estimates for patients with ECOG 0-1 with ES-SCLC treated with CE from the Flatiron Health Database, which was a longitudinal database from over 280 cancer clinics and 2.2 million active US cancer patients.</p> <p>Comparison of proportion alive in patients treated with CE based on extrapolation and the Flatiron database</p> <table border="1" data-bbox="352 703 1007 965"> <thead> <tr> <th></th> <th>1 year</th> <th>2 year</th> <th>3 year</th> <th>5 year</th> </tr> </thead> <tbody> <tr> <td>Flatiron</td> <td>35.6%, 281 at risk</td> <td>12.0%, 63 at risk</td> <td>5.4%, 15 at risk</td> <td>4.8%, 1 at risk</td> </tr> <tr> <td>Exponential</td> <td>38.2%</td> <td>14.3%</td> <td>6.2%</td> <td>1.2%</td> </tr> <tr> <td>Weibull</td> <td>38.2%</td> <td>4.5%</td> <td>0.2%</td> <td>0%</td> </tr> <tr> <td>Log logistic</td> <td>38.2%</td> <td>11.2%</td> <td>4.9%</td> <td>1.6%</td> </tr> <tr> <td>Log normal</td> <td>38.2%</td> <td>14.5%</td> <td>7.4%</td> <td>2.6%</td> </tr> <tr> <td>Gamma</td> <td>38.2%</td> <td>3.0%</td> <td>0%</td> <td>0%</td> </tr> <tr> <td>Gompertz</td> <td>38.2%</td> <td>0.7%</td> <td>0%</td> <td>0%</td> </tr> </tbody> </table> <p>Shaded cell indicates base case Source: Table 3.4.2, Section 3 Economic evaluation.xlsx</p> <p>However, the Flatiron Health Database was based on only a small number of patients at risk at Years 3 and 5. Further, the applicability of patients in the Flatiron database to those enrolled in IMpower 133 was unclear. For example, patients enrolled in IMpower 133 may be healthier than patients in Flatiron, as the trial excluded patients with some comorbidities and were generally younger (median age of patients in IMpower 133 was 64 years compared to 67 years in Flatiron). Therefore, it is possible that the survival of patients in Flatiron may be worse than patients enrolled in IMpower 133 (as observed at the 1 year mark) and using Flatiron as a 'benchmark' may underestimate survival in the comparator arm and favour atezolizumab + CE. The log normal extrapolation, which estimates a slightly higher survival at 2 and 3 years compared to Flatiron, may be an appropriate extrapolation for patients treated with CE only in IMpower 133.</p>		1 year	2 year	3 year	5 year	Flatiron	35.6%, 281 at risk	12.0%, 63 at risk	5.4%, 15 at risk	4.8%, 1 at risk	Exponential	38.2%	14.3%	6.2%	1.2%	Weibull	38.2%	4.5%	0.2%	0%	Log logistic	38.2%	11.2%	4.9%	1.6%	Log normal	38.2%	14.5%	7.4%	2.6%	Gamma	38.2%	3.0%	0%	0%	Gompertz	38.2%	0.7%	0%	0%	<p>High, favours atezolizumab. Using Weibull functional form for OS in both treatment arms leads to an increase in ICER by █%. Using the log normal function for OS in the 'CE only' arm (but maintaining the log logistic extrapolation in the atezolizumab+ CE arm) increases ICER by █%.</p>
	1 year	2 year	3 year	5 year																																						
Flatiron	35.6%, 281 at risk	12.0%, 63 at risk	5.4%, 15 at risk	4.8%, 1 at risk																																						
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Gompertz	38.2%	0.7%	0%	0%																																						
Time horizon	Treatment effect continued beyond median follow up of 13.9 months in IMpower 133 (22.9 months in the January 2019 data-cut) for up to 5 years.	High, favours atezolizumab. Going from trial based duration (13.9 months, ICER = more than \$200,000/QALY) decreased ICER by more than █% (5 years, ICER = \$75,000/QALY - \$105,000/QALY)																																								
Survival convergence	The submission does not assume any survival convergence in the base case, and the benefit in IMpower 133 was assumed to persist for 5 years	High, favours atezolizumab. Assuming survival convergence at 5 years, starting at 24 months, the ICER increases by █%.																																								

Description	Method/Value	Impact
Estimation of time on treatment	The base case model uses TTTD curve to estimate whether patients remain on treatment rather than PFS, which would be more consistent with the proposed PBS restriction (i.e. if the restriction allows continuation in patients who are stable and responding, rather than requiring patients to discontinue once they progress).	Moderate, favours atezolizumab. Using PFS to estimate patients on treatment instead of TTTD increases ICER by ██████%

Source: constructed during evaluation.

6.51 The results of the stepped economic evaluation are presented in Table 12.

Table 12: Results of the stepped economic evaluation

Step and component	Atezolizumab + CE	CE only	Increment
Step 1 Trial-based analysis up to 13.9 months			
Costs	\$ ██████	\$ ██████	\$ ██████
LY	██████ LY	██████ LY	██████ LY
QALY	██████ QALY	██████ QALY	██████ QALY
Incremental cost/extra LY gained			\$ ██████
Incremental cost/extra QALY gained			\$ ██████
Step 2: Parametric extrapolation from 13.9 months to a 5 year time horizon			
Costs	\$ ██████	\$ ██████	\$ ██████
LY	██████ LY	██████ LY	██████ LY
QALY	██████ QALY	██████ QALY	██████ QALY
Incremental cost/extra LY gained			\$ ██████
Incremental cost/extra QALY gained			\$ ██████
Step 3/4: Inclusion of medical resource use costs and convert to QALY			
Costs	\$ ██████	\$ ██████	\$ ██████
LY	██████ LY	██████ LY	██████ LY
QALY	██████ QALY	██████ QALY	██████ QALY
Incremental cost/extra LY gained			\$ ██████
Incremental cost/extra QALY gained			\$ ██████
Step 5: Inclusion of end of life costs			
Costs	\$ ██████	\$ ██████	\$ ██████
QALY	██████ QALY	██████ QALY	██████ QALY
Incremental cost/extra QALY gained			\$ ██████ /QALY

Source: Economic Evaluation.xlsx 'Results'

6.52 The base case ICER of \$75,000/QALY - \$105,000/QALY is relatively high, and likely to be uncertain as it was derived by extrapolation from data at 13.9 months. The ICER at the trial based duration of 13.9 months was more than four times greater, at more than \$200,000/QALY, indicating that there is significant uncertainty with the extrapolation method.

6.53 Sensitivity analyses around the economic evaluation are presented in Table 13.

Table 13: Sensitivity analysis presented in the submission

	Incremental cost	Incremental effectiveness (QALYG)	Incremental cost per QALYG	Percentage change from base case
Base-case	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]%
Survival convergence at 60 months starting at 48 months	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]%
Survival convergence at 60 months starting at 24 months	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]%
Survival convergence at 60 months starting at 13.9 months	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]%
Utility values based on health state rather than time to death. PFS (0.72) and Progressed disease (0.70)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]%
Additional sensitivity analyses conducted during evaluation				
Using PFS to determine patients on treatment (base case TTTD) ¹	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]%
Using PFS to determine patients on treatment and (pooled) utility (base case TTTD and proximity to death used) ¹	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	+ [REDACTED]%
Assume no difference in PFS (i.e. PFS in Atezolizumab CE = PFS CE only)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]%
Weibull extrapolation for OS for both treatment arms (base case log log) ²	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]%
Log normal extrapolation for OS in 'CE only' arm, log in atezolizumab + CE arm (base case log in both arms) ³	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]%
Multivariate sensitivity analyses conducted by ESC				
-Weibull OS in both arms, - convergence starting at 24 months, - utilities based on health state (PFS = 0.72; PD = 0.70) ²	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]%
As above, plus using PFS to determine patients on treatment (rather than TTTD) to reflect proposed restriction ^{1,2}	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]%

¹ Replace half cycle adjusted time to off treatment estimates for both atezolizumab and CE with discounted half cycle PFS curve estimates for the respective treatment arms

² Weibull functional form had the lowest AIC/BIC amongst all parametric functions for fitting of OS

³ Potentially more plausible to account for patients in IMpower 133 being younger and healthier than patients in Flatiron database

⁴ Time points at which approximately 50% of patients remain at risk for progression/discontinuation.

Text in italics indicate values or sensitivity analyses conducted during evaluation using Economic Evaluation.xlsx

Source: Table 3.9.1, p46 Section 3A of the submission

The redacted table shows ICERs in the range of \$75,000/QALY - \$105,000/QALY and more than \$200,000/QALY.

6.54 The range of sensitivity analyses show that even in the most optimistic scenario presented by the submission (e.g. time horizon of 20 years) the ICER is likely to be high (\$75,000/QALY - \$105,000/QALY).

6.55 The ESC considered a plausible alternative scenario could comprise the following: a time horizon of 5 years (as presented in the base case); convergence of survival curves at 60 months with convergence commencing at 24 months; and parametric extrapolation of OS based on the Weibull function in both treatment arms. The ESC noted that this resulted in an ICER of \$105,000/QALY - \$200,000/QALY. The ESC noted that this ICER would further increase to more than \$200,000/QALY if treatment duration was based on PFS rather than time to treatment discontinuation, which may reflect usage if the restriction allows continuation in patients who are stable and responding as proposed by the submission (because use of PFS data would lead to a

longer duration of treatment). The sponsor stated in the Pre-PBAC response that there is limited scope to implement any substantial revisions to the modelling parameters explored in the commentary and ESC Advice, and maintained the base case ICER within the range of \$75,000 to \$105,000 to be appropriate.

Drug cost/patient: \$ [REDACTED] (based on the mean duration in the economic model)

Table 14: Drug cost per patient for atezolizumab

	Atezolizumab Trial dose and duration	Atezolizumab Model	Atezolizumab Financial estimates
Mean dose	1,200mg	1,200mg	1,200mg
Mean duration	[REDACTED] months	[REDACTED] months	[REDACTED] months
Mean number of doses ^a	[REDACTED]	[REDACTED]	[REDACTED]
Cost/patient/dose		\$ [REDACTED]	
Cost/patient	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

^a assumed 1 dose every 3 weeks

Source: Table 35, p141 IMpower CSR, p43 Section 3A and Table 4.2.8, p13 and Table 4.2.11, p15 Section 4 of the submission

6.56 The model estimated a duration of [REDACTED] weeks which translates to [REDACTED] average doses and a corresponding effective cost of \$ [REDACTED] per patient. The difference between the mean duration of treatment in the trial versus the model/financial estimates is due to the model extrapolation from 13.9 months to 5 years.

Estimated PBS usage & financial implications

6.57 This submission was considered by DUSC.

6.58 The submission used an epidemiological approach to estimate the financial impacts of listing. Data reported by AIHW and from Australian hospital registries were used to estimate the incidence and prevalence of ES- and LS-SCLC in Australia.

6.59 The financial estimates from the submission are summarised in Table 15. The results presented below reflect the values calculated during the evaluation; ie, using the number of patients in the current calendar year to estimate prevalent patients in the same year.

Table 15: Summary of financial estimates

	2020	2021	2022	2023	2024	2025
Lung cancer patients ^a	13,219	13,491	13,762	14,034	14,305	14,577
SCLC patients ^b	1,553	1,585	1,617	1,649	1,681	1,713
ES-SCLC (incident patients) ^c	1,108	1,131	1,153	1,176	1,199	1,222
ECOG 0-1 ^d	█	█	█	█	█	█
LS SCLC developing into ES-SCLC (prevalent patients) ^e	█	█	█	█	█	█
ECOG 0-1 ^f	█	█	█	█	█	█
Grandfathered patients ^g	█	█	█	█	█	█
Total treated patients	█	█	█	█	█	█
Number of initiative doses ^h	█	█	█	█	█	█
Number of continuing doses ⁱ	█	█	█	█	█	█
Total atezolizumab volume	█	█	█	█	█	█
Cost to PBS/RPBS	█	█	█	█	█	█
Copayments ^j	█	█	█	█	█	█
Net cost to PBS/RPBS	█	█	█	█	█	█
Number of administrations in private hospital ^k	█	█	█	█	█	█
Cost to MBS for item number 13915 (85% rebate)	█	█	█	█	█	█
Net cost to Government	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

SCLC = small cell lung cancer, ES = extensive stage, ECOG = Eastern Cooperative Oncology Group performance status, LS = localised stage

^a Extrapolated from data reported by Australian Institute of Health and Welfare

^b Estimate 11.75% of all lung cancer patients have SCLC, constant each year

^c Assumed 71.34% of all SCLC to be ES-SCLC

^d Assumed █ of ES-SCLC patients had ECOG 0-1

^e Assumed █ of all LS SCLC patients (█% of all SCLC patients) develop ES-SCLC

^f Assumed all patients who develop ES-SCLC from LS SCLC will have ECOG 0-1

^g Assumed █ patients will enrol before listing to an access program scheduled to begin November 2019 and will transition to PBS reimbursed treatment in year 1

^h Assume █ doses for all patients, minus █ initiation doses for grandfathered patients in year 1 only

ⁱ Assumed █ doses for all patients, based on average doses from economic model

^j Estimated by dividing initiation doses by █ and continuing doses by █ and applying \$16.43 copayment

^k Only continuing treatment in private hospital (65.74%) attracts MBS administration fees. Assume 100% of patients are treated as outpatients.

Source: Table 4.2.2, p9, table 4.2.4 and 4.2.5, p10, table 4.2.6, p11, 4.2.7, p12, 4.2.8, p13, table 4.2.12, p17, table 4.5.3, p21 and table 4.5.4 p 22, Section 4 of the submission.

6.60 The submission estimated that the cost of listing atezolizumab, when used in conjunction with CE, in patients with ES-SCLC and ECOG 0-1 will be around from \$20-\$30 million in the first year of listing, increasing to \$30-\$60 million by Year 6. This included less than 10,000 grandfathered patients in Year 1, and was based on the assumption of █ doses of atezolizumab per patient (█ initiating and █ continuing). The DUSC noted the patient access program had not yet commenced, however considered that it was reasonable to include grandfathered patients in the estimates for Year 1 (2019).

6.61 The evaluation noted there were several assumptions which may have resulted in the financial estimates being overestimated, including:

- The assumption that incidence of SCLC will be constant over time: Given that SCLC is closely linked to smoking and there is evidence that the rate of smoking is

declining, it is possible for the incidence of SCLC to also decline over time. The DUSC discussed that due to decreasing rates of heavy smoking, the proportion of SCLC would likely be decreasing relative to NSCLC. It was reported that the proportion of SCLC in 1986 was 17.3%, and decreased to 12.95% in 2002 (Govindan 2006). Overall, the DUSC agreed that the incidence of SCLC may decrease over time, but considered the submission's estimate of 11.75% incidence of lung cancers were SCLC (AIHW 2011) to be reasonable.

- The assumption that 100% of LS-SCLC patients would be eligible for atezolizumab after progression (i.e. have ECOG 0-1): This was based on 'expert opinion' and may not be appropriate. The DUSC agreed with the evaluation, that it was unlikely 100% of patients who progress from LS-SCLC to ES-SCLC will have ECOG 0-1, and considered the proportion was more likely to be [REDACTED]. The pre-PBAC response accepted this change.
- The assumption that [REDACTED] of patients with ES-SCLC would be eligible for atezolizumab, when an alternative source identified indicated it may be [REDACTED]. The DUSC considered that although the submission used the upper estimate to determine the proportion of ES SCLC with ECOG 0-1, this estimate was reasonable.

6.62 The submission assumed 100% of eligible patients would use atezolizumab from year 1. The DUSC agreed that uptake would be high given the lack of novel treatments for SCLC, but noted some patients with medical contraindications, such as active autoimmune diseases, would prevent them from being treated with immunotherapies. The DUSC considered the estimated uptake rate in incident and prevalent patients should be reduced to [REDACTED]%. The pre-PBAC response accepted this change.

6.63 Table 16 summarises the estimates incorporating the changes suggested by DUSC. These revised estimates were accepted in the Pre-PBAC response .

Table 16: Summary of financial estimates including changes suggested by DUSC (accepted in the pre-PBAC response)

	2020	2021	2022	2023	2024	2025
Lung cancer patients	13,219	13,491	13,762	14,034	14,305	14,577
SCLC patients	1,553	1,585	1,617	1,649	1,681	1,713
ES SCLC (incident patients)	1,108	1,131	1,153	1,176	1,199	1,222
ECOG 0-1	█	█	█	█	█	█
Patients electing treatment ^a	█	█	█	█	█	█
LS SCLC developing into ES SCLC (prevalent patients)	█	█	█	█	█	█
ECOG 0-1 ^b	█	█	█	█	█	█
Patients electing treatment ^a	█	█	█	█	█	█
Grandfathered patients ^c	█	█	█	█	█	█
Total treated patients	█	█	█	█	█	█
Number of initiative doses	█	█	█	█	█	█
Number of continuing doses	█	█	█	█	█	█
Total atezolizumab volume	█	█	█	█	█	█
Cost to PBS/RPBS	█	█	█	█	█	█
Copayments	█	█	█	█	█	█
Net cost to PBS/RPBS	█	█	█	█	█	█
Number of administrations in private hospital	█	█	█	█	█	█
Cost to MBS for item number 13915 (85% rebate)	█	█	█	█	█	█
Net cost to Government	█	█	█	█	█	█

Source: Section 4 Workbook of the submission, recalculated by DUSC.

^a Assumes █% of eligible patients will be treated.

^b Assumes █% of patients progressing from LS-ECOG to ES-ECOG are ECOG 0-1.

^c Assumes █% of grandfathered patients will be treated.

Quality use of medicines

6.64 No information was provided in the submission on quality use of medicines; however, DUSC commented the toxicity management guidelines for immunotherapies are relatively well established.

6.65 The DUSC considered that there is a risk of use of atezolizumab outside the proposed PBS restriction in patients with ECOG greater than one, but that this risk is likely small. Additionally, there may be a risk of use of atezolizumab as an adjuvant therapy following treatment for LS-SCLC, and for treatment of high-grade neuroendocrine

carcinomas of non-pulmonary origin (for example small bowel or pancreatic neuroendocrine carcinomas).

Financial Management – Risk Sharing Arrangements

- 6.66 The sponsor proposed a risk-sharing arrangement (RSA) based on a subsidisation cap and rebate arrangement to reduce uncertainty. The value of the proposed cap was based on the submission's financial estimates for each year.
- 6.67 The ESC considered that an RSA would be required given the potential for leakage outside the PBS restriction in patients with non-lung neuroendocrine carcinomas and following curative-intent treatment for LS-SCLC.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend atezolizumab for the treatment of previously untreated extensive stage (ES) small cell lung cancer (SCLC). The PBAC noted the high clinical need for effective treatments in this therapeutic area. The PBAC considered the evidence presented demonstrated there was a modest improvement in overall survival (OS) with atezolizumab. Although the PBAC considered this change to be clinically meaningful, the PBAC noted the magnitude and durability of this benefit was uncertain and the impact on patient quality of life was unclear. The PBAC also considered the ICER in this setting was uncertain and unacceptably high at the proposed price.
- 7.2 The PBAC noted that there is a clinical need for effective treatments in SCLC given the poor prognosis and that there have been no new developments in the treatment of SCLC in 20 years. The PBAC noted this was supported by the consumer comments received for this submission.
- 7.3 The PBAC considered that the requested restriction was reasonable and consistent with the clinical trial evidence. The PBAC considered that if atezolizumab was listed for previously untreated ES-SCLC, the following should be included:
- either cisplatin or carboplatin should be allowed as platinum based chemotherapy under the initial restriction to allow patients on either chemotherapy to be treated with atezolizumab;
 - ECOG performance score of 1 or less should be included in the initial and grandfather restrictions; and
 - a stopping rule should be included in the continuing restriction so patients who have developed disease progression cannot continue being treated with atezolizumab. This aligns with the continuing restriction for other PD-L1 drugs.
- 7.4 The PBAC considered the nominated comparator in the submission, platinum based chemotherapy (cisplatin or carboplatin) + etoposide, to be acceptable.

- 7.5 The submission was based on one head-to-head randomised, Phase I/III, double-blind, multi-centre trial (IMpower 133; N=403) comparing atezolizumab + CE (followed by atezolizumab monotherapy) and placebo + CE (or CE only) in patients with previously untreated ES-SCLC.
- 7.6 The PBAC noted that a modest (2.0 months median increase), but statistically significant improvement in OS for patients treated with atezolizumab + CE compared to patients treated with placebo + CE was demonstrated in the IMpower 133 trial. As such, the PBAC considered that the claim of superior comparative effectiveness of atezolizumab + CE compared with CE only was reasonable with respect to OS. However, the PBAC considered that the magnitude and durability of the benefit was uncertain, especially given the short duration of follow-up in the trial (median follow-up of 22.9 months in the updated data-cut) and the aggressive nature of ES-SCLC. The PSCR stated that no further formal OS analyses of IMpower 133 are planned. Thus, it was unlikely that these uncertainties with the OS data would be resolved through any further data-cuts.
- 7.7 In terms of PFS, IMpower 133 demonstrated a modest, but statistically significant improvement in PFS for patients treated with atezolizumab + CE compared to patients treated with placebo + CE. The PBAC considered it was unclear if the magnitude of difference in PFS (0.9 months median increase) between atezolizumab + CE and placebo + CE was clinically meaningful.
- 7.8 The PBAC considered that the evidence provided in the submission did not support the submission's claim that treatment with atezolizumab + CE improved quality of life compared to CE only. The clinical trial data included patient reported quality of life outcomes based on the EORTC QLQ-C30 and QLC-LC13 questionnaires. However, no statistical tests were conducted around these results, therefore it is unclear if any differences in the subscales in the questionnaires were clinically meaningful. Also, there was insufficient information presented about the EQ-5D results to enable meaningful analysis. Thus, the PBAC considered the submission's claim that the benefit in OS would represent a grade 4 benefit (out of 5) on the European Society for Medical Oncology's Magnitude of Clinical Benefit Scale (indicating a 'high level of proven clinical benefit') was not supported.
- 7.9 The PBAC noted that patients treated with atezolizumab + CE were statistically significantly more likely to experience a range of AEs compared to patients treated with placebo + CE in IMpower 133. Therefore, the PBAC accepted the revised claim that atezolizumab + CE is inferior to CE alone in terms of comparative safety. The PBAC considered that it is likely that the range of AEs associated with atezolizumab treatment reported in IMpower 133 were not exhaustive, and more AEs may be reported as more patients are treated with atezolizumab.
- 7.10 A pre-specified subgroup analysis from the April 2018 cutoff showed that treatment with atezolizumab + CE resulted in statistically significantly improved OS compared to placebo + CE in patients who were aged 65 or more but not in patients aged less than

65 years. The PBAC considered that the benefit of atezolizumab in the <65 years age group was uncertain.

- 7.11 The submission presented a cost utility analysis using a stepped economic evaluation based on the IMpower 133 trial. The PBAC noted the PSCR and pre-PBAC response provided updated clinical data from the January 2019 cutoff, however the model results were not updated to include these updated data. The PBAC considered that the economic model would need to be updated to reflect the most recent data-cut.
- 7.12 The PBAC noted that the economic model had assumed a continued treatment effect over the duration of the time horizon, and considered this was not reasonable as the durability of the gain in survival was unclear given the uncertain magnitude of the OS benefit, the aggressive nature of ES-SCLC and the relatively short duration of follow-up (even with the updated data-cut). Thus, the PBAC considered that the base case of the economic model should: (i) assume the OS curves begin to converge at 24 months with convergence at 60 months; and (ii) use a time horizon of 5 years (as presented in the base case). The PBAC noted this increased the ICER to \$105,000/QALY - \$200,000/QALY.
- 7.13 The PBAC noted and agreed with the other issues regarding the economic model that were identified by the evaluation and the ESC (as outlined in the 'Economic analysis' section), particularly the issues regarding the: choice of parametric function for OS extrapolation (per Paragraphs 6.44-6.46); and the proximity to death utilities presented (per Paragraph 6.48). In light of these uncertainties, along with the small OS benefit and unclear PFS benefit, the PBAC considered that an ICER less than \$70,000 per QALY (using the base case outlined in the paragraph above) would be required for atezolizumab to be considered suitably cost-effective.
- 7.14 The PBAC considered that the estimated PBS population was likely overestimated in the resubmission. The PBAC considered the changes to the financial estimates that were proposed by DUSC, and accepted by the pre-PBAC response, were reasonable including reducing the proportion of patients who progress from LS-SCLC to ES-SCLC and who have a ECOG 0-1 to ■%; and reducing the estimated uptake rate in incident and prevalent patients to ■% (due to contraindications).
- 7.15 The submission proposed an RSA based on a subsidisation cap and rebate arrangement to reduce uncertainty around the financial impact. The PBAC considered that an RSA with a 100% rebate above the subsidy caps would be required to account for the uncertain patient numbers and potential for leakage.
- 7.16 The PBAC considered that any resubmission would need to be a major submission and should address the following issues: (i) update the economic model based on the most recent data-cut and using the base case outlined in Paragraph 7.12; (ii) a price reduction would be required to achieve an ICER of less than \$70,000 per QALY; and (iii) a risk sharing arrangement would be required with 100% rebates for expenditure above the caps.

7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

Roche is disappointed with the outcome given the genuine unmet need for a new treatment option that can prolong survival in patients with extensive-stage small cell lung cancer. Roche is committed to working with the PBAC to ensure that Australian patients with extensive-stage SCLC can access atezolizumab at the earliest opportunity.