5.07 LURBINECTEDIN, Powder for I.V. infusion 2 mg, Powder for I.V. infusion 4 mg, Zepzelca®, Specialised Therapeutics Pharma Pty Ltd

1 Purpose of submission

1.1 The Category 1 submission requested a Section 100 Efficient Funding of Chemotherapy, Authority Required (STREAMLINED) listing for lurbinectedin for use in combination with atezolizumab for first-line maintenance treatment of extensive-stage small cell lung cancer (ES-SCLC) for patients who have not progressed on or after first line induction therapy with atezolizumab, a platinum-based antineoplastic drug, and etoposide.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus atezolizumab monotherapy.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Extensive-stage small cell lung cancer that has not progressed on or after first-line induction therapy with atezolizumab, a platinum-based antineoplastic drug, and etoposide.
Intervention	Lurbinectedin + atezolizumab (maintenance therapy).
Comparator	Atezolizumab (maintenance therapy).
Outcomes	Progression free survival, overall survival, objective response rate, duration of response, time to confirmed deterioration, quality of life, adverse events.
Clinical claim	Lurbinectedin + atezolizumab (maintenance therapy) is superior in terms of efficacy and inferior in terms of safety compared to atezolizumab (maintenance therapy).

Source: Table 1, p17 of the submission.

2 Background

Registration status

2.1 Lurbinectedin 4 mg (powder for injection) was submitted under the TGA/PBAC parallel process, with US Federal Drug Administration (FDA) international collaboration via Project Orbis, for the following indication: in combination with atezolizumab, for the maintenance treatment of ES-SCLC in adult patients whose disease has not progressed after first line induction therapy with atezolizumab, carboplatin and etoposide.

2.2 The pre-PBAC response stated that the submission for the 2 mg formulation was submitted to the TGA in October 2025.

2.3 At the time of PBAC consideration, no TGA documents were available.

2.4 Lurbinectedin 4 mg (powder for injection) has provisional TGA approval for the treatment of patients with metastatic SCLC that has progressed on or after prior platinum-containing therapy (13 September 2021), based on the results of a single

arm trial (Study B-005), with continued approval dependent on verification of clinical benefit in the confirmatory LAGOON trial.

Previous PBAC considerations

2.5 This is the first time lurbinectedin has been considered by the PBAC for listing on the PBS.

2.6 The PBAC recommended durvalumab for the treatment of limited-stage small cell lung cancer in patients whose disease has not progressed during or following chemoradiation therapy (CRT) at the November 2020 PBAC meeting[1].

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

3 Requested listing

3.1 Secretariat suggested additions are in italics and deletions are in strikethrough.

[1] Available at: durvalumab-psd-nov-2020.pdf

MEDICINAL PRODUCT Form	DPMQ	Max. Amount	№.of Rpts
LURBINECTEDIN Injection	**Published** Public: $[redacted] Private: $[redacted] **Effective** Public: $[redacted] Private: $[redacted]	8mg	4
Available brands			
Zepzelca (lurbinectedin 2 mg powder for solution for IV infusion, vial)			
Zepzelca (lurbinectedin 4 mg powder for solution for IV infusion, vial)			
Restriction Summary [new1]/ Treatment of Concept: [new1A]			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: Medical Practitioners			
Restriction type: Authority Required (STREAMLINED) [NEW]			
Episodicity: [blank]			
Severity: [blank]			
Condition: Extensive-stage small cell lung cancer			
Indication: Extensive-stage small cell lung cancer			
Treatment Phase: Maintenance therapy-			
Clinical criteria:			
Patient must have previously received PBS-subsidised treatment with atezolizumab, a platinum-based antineoplastic drug and etoposide as induction for this condition.			
Clinical criteria:			
Patient must not have developed disease progression while being treated with atezolizumab, a platinum-based antineoplastic drug and etoposide as induction for this condition.			
AND			
Clinical criteria:			
Patient must not have developed disease progression while being treated with this drug for this condition			
AND			
Clinical criteria:			
Treatment must be ~~initiated~~ in combination therapy with atezolizumab for this condition; or			
Patient must have developed an intolerance/toxicity to atezolizumab preventing the use of combination therapy			
Prescribing instruction: The patient's body surface area must be documented in the patient's medical records at the time treatment is initiated.			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Administrative Advice: Special Pricing Arrangements apply.			

3.2 The submission requested a special pricing arrangement, with an effective ex-manufacturer price (EMP) for lurbinectedin 2 mg of $[redacted] per vial, and an effective EMP for lurbinectedin 4 mg of $[redacted] per vial. The proposed effective EMP of the 2 mg vial was reduced to $[redacted] in the pre-PBAC response (the economic and financial models were based on the price of the 2 mg vial).

3.3 The proposed maximum amount of lurbinectedin (8 mg) with 4 repeats is sufficient for 3 months of maintenance treatment, assuming an average body surface area (BSA) of 1.83 m^2 and an equivalent maximum dose of 5.9 mg per course of treatment.

3.4 The proposed restriction is less specific in terms of prior induction therapy (atezolizumab, a platinum-based antineoplastic drug and etoposide) compared to the

proposed TGA indication (atezolizumab, carboplatin and etoposide) but it is consistent with the current PBS listings for atezolizumab and durvalumab in ES-SCLC post-induction maintenance therapy.

3.5 The proposed restriction is broader than the key clinical trial (IMforte) eligibility criteria, which required patients to have completed induction therapy (rather than received) and maintained Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1 status to be eligible for randomisation into the maintenance treatment phase, and excluded patients with central nervous system metastases.

3.6 The submission included a grandfathering restriction for patients receiving non-PBS funded lurbinectedin as part of the sponsor's special access program, to transition to PBS subsidised lurbinectedin, with an estimated 50 eligible patients.

3.7 The current atezolizumab PBS listing for ES-SCLC in the maintenance setting includes specific items for 3-weekly and 4-weekly treatment regimens. Given the administration of lurbinectedin is 3-weekly, the submission assumed that any use of atezolizumab because of the lurbinectedin listing would only affect the atezolizumab 3-weekly regimen listing.

3.8 The ESC noted that patients receiving first-line induction therapy with PBS subsidised durvalumab would not be eligible for adjunctive lurbinectedin maintenance therapy under the proposed restriction or TGA indication. The PBAC previously considered durvalumab was non-inferior to atezolizumab in initial (induction) and continuing (maintenance) treatment of ES-SCLC, and recommended durvalumab on a cost-minimisation basis versus atezolizumab (paragraph 7.1, durvalumab Public Summary Document [PSD], November 2020 PBAC meeting). Both atezolizumab and durvalumab monotherapy were replaced by lurbinectedin plus atezolizumab in the submission's estimated financial impact to the PBS.

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

4 Population and disease

4.1 SCLC is an aggressive, poorly differentiated neuroendocrine lung cancer, characterised by rapid proliferation and early widespread metastases. SCLC accounts for approximately 10-14% of all lung cancer diagnoses.

4.2 Most ES-SCLC patients are symptomatic at diagnosis, reporting substantial impairment of physical, cognitive, emotional, and social functioning, and a broad range of disease and/or metastases related symptoms (dyspnoea, chest pain, cough, fatigue, anorexia, weight loss, bone pain, neurological symptoms, depression, anxiety; Sugimura et al. 2006)[2].

4.3 ES-SCLC is highly sensitive to initial systemic platinum-based chemotherapies, but progressive or relapsed disease is common, with a median survival of ≤10 months and a 5-year survival of approximately 2% (National Cancer Institute 2025[3]; Reck 2024[4]). The introduction of immunotherapies in combination with first-line platinum-based chemotherapies has improved median overall survival to approximately 12.3 months with atezolizumab (IMpower133 trial) and 13.0 months with durvalumab (CASPIAN trial; paragraph 6.08, durvalumab PSD, November 2020 PBAC meeting)[5].

4.4 Lurbinectedin is a synthetic alkylating agent that inhibits oncogenic transcription, promoting cancer cell death. The ESC noted lurbinectedin is a chemotherapy agent and its use in the maintenance treatment setting effectively extends the duration of treatment with chemotherapy.

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

5 Comparator

5.1 The submission nominated atezolizumab monotherapy as the main comparator. The main argument provided in support of this nomination was that lurbinectedin is proposed as an add-on to atezolizumab maintenance immunotherapy in patients responding to first-line treatment with a platinum-based chemotherapy regimen with etoposide in combination with an immunotherapy.

5.2 The submission acknowledged that both atezolizumab and durvalumab are preferred immunotherapy options for first-line induction and subsequent maintenance therapy for ES-SCLC but noted that PBS services for the 2024 calendar year showed low uptake of durvalumab for both induction (8%) and maintenance therapy (4%) compared with atezolizumab (92% and 96% respectively). The submission argued that atezolizumab is the therapy most likely to be replaced by lurbinectedin plus atezolizumab in the proposed population. The ESC noted that the proposed restriction for lurbinectedin specified use should follow an atezolizumab-based induction.

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[2] Sugimura H, Yang P. Long-term Survivorship in Lung Cancer: A Review. *Chest* 2006; 129(4):1088-1097.

[3] https://www.cancer.gov/types/lung/patient/small-cell-lung-treatment-pdq

[4] Reck et al. IMpower133: Updated overall survival (OS) analysis of first-line (1L) atezolizumab (atezo) + carboplatin + etoposide in extensive-stage SCLC (ES-SCLC). *Annals of Oncology* 2019; 30: v710-v711

[5] https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/recommendations-made-by-the-pbac-november-2020.

5.3 The Pre-Sub-Committee Response (PSCR) noted that the most recent NCCN guidelines for SCLC (version 2.2026 – September 16, 2025) includes lurbinectedin with atezolizumab as a preferred primary maintenance therapy for ES-SCLC. This recommendation was based on the results from the IMforte trial and establishes lurbinectedin plus atezolizumab as a new standard of care internationally for these patients. Current Australian guidelines do not include the use of lurbinectedin in first-line chemotherapy regimens for ES-SCLC.

5.4 Treatment options for patients with disease progression on or after prior platinum-containing induction therapy include retreatment with a platinum-based chemotherapy, as well as novel therapies as part of a clinical trial. Lurbinectedin has a provisional TGA listing for patients who have progressed on or after prior platinum-containing induction therapy and is recommended as a treatment option for patients with relapsed SCLC in the NCCN (2026), ASCO (2025)[6] and ESMO (2021)[7] guidelines.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician highlighted the need for effective first line treatments, noting the aggressive nature of ES-SCLC, which leads to poor outcomes for patients. The clinician outlined how the drug would be used in practice and discussed the results of the IMforte trial. The clinician also noted that lurbinectedin is used internationally as monotherapy in the second-line setting. The PBAC considered the hearing informative.

Consumer inputs

6.2 The PBAC noted and welcomed the input from health care professionals (13) and organisations (4) via the Office of Health Technology Assessment Consultation Hub. The input from the health professionals noted the high unmet need for effective ES-SCLC treatments, highlighting the aggressive nature of the disease, limited treatment options, poor prognosis and high mortality rates. The input noted that while current first-line treatment is initially effective, progression of the disease is inevitable, and existing second-line chemotherapies have low response rates (approximately 10-20%)

[6] ASCO. 2025. Tarlatamab versus chemotherapy (CTx) as second-line (2L) treatment for small cell lung cancer (SCLC): Primary analysis of Ph3 DeLLphi-304. https://www.asco.org/abstracts-presentations/ABSTRACT487828.
[7] Dingemans et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2021; 32(7): 839-853.

and limited effectiveness. The health professionals noted that adding maintenance lurbinectedin to atezolizumab, (after completion of first-line chemotherapy), significantly improves progression-free survival and overall survival, describing this combination as an incremental step forward in ES-SCLC therapy and stated that even modest improvements in survival are meaningful and allow patients to manage personal affairs. The input noted that lurbinectedin has a tolerable safety profile.

6.3 The PBAC noted the advice received from Lung Foundation Australia, which stated that improving prognosis is one of the most important outcomes of lung cancer medications for patients. The PBAC also noted the advice received from Rare Cancers Australia (RCA), which emphasised the sense of worry patients with ES-SCLC feel about their diagnosis, and the unfavourable side-effects of systemic therapies. The PBAC noted that the advice was supportive of the evidence provided in the submission.

6.4 The PBAC also noted the advice received from the Thoracic Group of Australia (TOGA), which noted that in a disease with such a poor prognosis, the IMforte study provided evidence to support a new maintenance option as SoC for patients who do not progress on induction therapy. The TOGA also noted that the modest benefit received from lurbinectedin plus atezolizumab must be considered in conjunction with the higher rates of haematologic and infections toxicities.

6.5 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the lurbinectedin submission, categorising it as one of the therapies of "high priority for PBS listing" based on the IMforte trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for lurbinectedin, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[8], based on a comparison with atezolizumab monotherapy.

Clinical trials

6.6 The submission was based on one randomised, controlled trial comparing lurbinectedin, in combination with atezolizumab, to atezolizumab monotherapy as a maintenance treatment for ES-SCLC in adult patients whose disease had not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide (IMforte trial).

6.7 Details of the IMforte trial are provided in Table 2.

[8] Cherny NI, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology*. 2017; 28:2340-2366.

Table 2: Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
IMforte (NCT05091567)	Primary CSR for the IMforte trial. A phase III, open-label study of maintenance lurbinectedin in combination with atezolizumab compared with atezolizumab in participants with extensive stage small cell lung cancer (IMforte). Paz-Ares L, et al. Efficacy and safety of first-line maintenance therapy with lurbinectedin plus atezolizumab in extensive stage small cell lung cancer (IMforte): a randomised, multicentre, open-label, phase 3 trial.	Clinical Study Report March 2025. *The Lancet*. 2025; 405(10495):2129-2143.

Source: Table 17, p45 of the submission.

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in economic model
Direct randomised trials						
IMforte	483	R, C, OL, MC study Median follow-up 15 months.	Unclear	Adults with ES-SCLC. Responders to first-line induction therapy with platinum-based chemotherapy + etoposide + atezolizumab. ECOG PS 0-1. CNS metastases excluded.	OS (interim), PFS, CORR, DOR, TTCD, QoL, Safety.	Patient characteristics, PFS, OS, mean duration of treatment, incidence of adverse event.

Source: Section 2 of the submission.

Abbreviations: C, controlled; CORR, confirmed objective response rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MC, multi-centre; OL, open label; OS, overall survival; PFS, progression-free survival; QoL, quality of life; R, randomised; TTCD, time to confirmed deterioration.

6.9 The risk of bias in the IMforte trial was unclear. The open label design may have impacted assessment of quality-of-life outcomes and assessment of response to treatment. However, this may have been mitigated using the centralised independent review of clinical data and trial integrity/safety oversight by an independent data monitoring committee.

6.10 The IMforte trial includes 2 treatment phases:

- Induction therapy (Phase 1): A single arm treatment phase including adults with treatment naïve ES-SCLC, measurable tumours (RECIST v1.1), and ECOG PS 0 or 1. Patients previously treated for LS-SCLC were included (4.1%), after a treatment-free interval of at least 6 months prior to diagnosis of ES-SCLC. Patients with CNS metastases, uncontrolled tumour-related pain, or uncontrolled pleural effusion were excluded. All enrolled patients received 4 cycles of first-line induction therapy with atezolizumab, carboplatin and etoposide.

- Maintenance therapy (Phase 2): Patients achieving ongoing treatment response or stable disease after completion of 4 × 21-day cycles of first-line induction therapy and maintained ECOG performance status 0 or 1, were randomised to receive lurbinectedin plus atezolizumab or atezolizumab monotherapy until disease progression or unacceptable toxicity. Patients with CNS metastases, uncontrolled tumour-related pain, uncontrolled pleural effusion or clinically significant adverse

events expected to interfere with study treatments, were excluded. Crossover between therapies was not permitted.

6.11 A total of 483/660 (73.2%) patients completed the induction therapy and were randomised to the lurbinectedin plus atezolizumab or atezolizumab monotherapy treatment arms at the commencement of the maintenance phase. Large proportions of patients discontinued treatment in both the lurbinectedin plus atezolizumab (n=197, 81.4%) and atezolizumab monotherapy (n=208, 86.7%) treatment arms.

6.12 Patients in the lurbinectedin plus atezolizumab arm reported less advanced ES-SCLC compared to atezolizumab monotherapy in terms of tumour size (T4: lurbinectedin + atezolizumab 50.8%; atezolizumab 58.8%) and metastases (M1c: 47.5%; 58.9%) at baseline.

6.13 The ESC also noted that the lurbinectedin plus atezolizumab arm population included a higher proportion of younger patients (<65 years; 49%) as compared to the atezolizumab only group (37%). It further observed that the overall IMForte trial cohort was unusually young (35% older than 65 and 9% older than 70 in the lurbinectedin and atezolizumab group). This was not considered to be reflective of the Australian population with ES-SCLC. Victorian Lung Cancer Registry data (2011–19) found a median age of diagnosis of SCLC of 69 years (Huang et al. 2023)[9] . The ESC also noted that some patients in the clinical trial had prior exposure to prophylactic cranial irradiation which is not routinely used in Australian clinical practice.

6.14 The dosing and administration of lurbinectedin and atezolizumab in the IMforte trial were broadly consistent with the related Product Information. A maximum of 2 lurbinectedin dose reductions (2.6 mg/m^2; 2 mg/m^2) were allowed during the randomised maintenance treatment phase. Lurbinectedin and atezolizumab treatment could be interrupted or discontinued independently from each other. Dose modifications were not permitted for atezolizumab, but treatment was temporarily or permanently suspended for the management of treatment related toxicity and immune mediated adverse events. The ESC noted that a median of 7 doses were given in the lurbinectedin plus atezolizumab group over 4.1 months and a median of 4 doses were given in the atezolizumab only group over 2.1 months.

6.15 All patients in the lurbinectedin plus atezolizumab treatment arm received prespecified anti-emetic treatment and primary G-CSF prophylactic medications in Cycle 1 of treatment. Premedication was not prespecified for patients in the IMforte maintenance phase atezolizumab monotherapy arm but was given in accordance with the atezolizumab Product Information. Substantially larger proportions of patients in

[9] Huang et al. Patterns of care for people with small cell lung cancer in Victoria, 2011–19: a retrospective, population-based registry data study. *Medical Journal of Australia*. 2023; 219(3):120-126.

the lurbinectedin plus atezolizumab treatment arm received concomitant premedications compared to the atezolizumab monotherapy arm.

Comparative effectiveness

6.16 Overall survival data available at the 29 July 2024 clinical cutoff date were presented as an interim analysis. To mitigate the potential impact on overall survival of non-protocol anti-cancer treatments following discontinuation of study treatment, the statistical stopping boundary for overall survival at the interim analysis was determined by the Hwang–Shih–DeCani α spending function, using the γ parameter of −1.5, and the actual number of overall survival events observed. Further analyses of overall survival data were not reported, and the sponsor advised that the results presented for the data cutoff of 29 July 2024 are considered final for regulatory purposes.

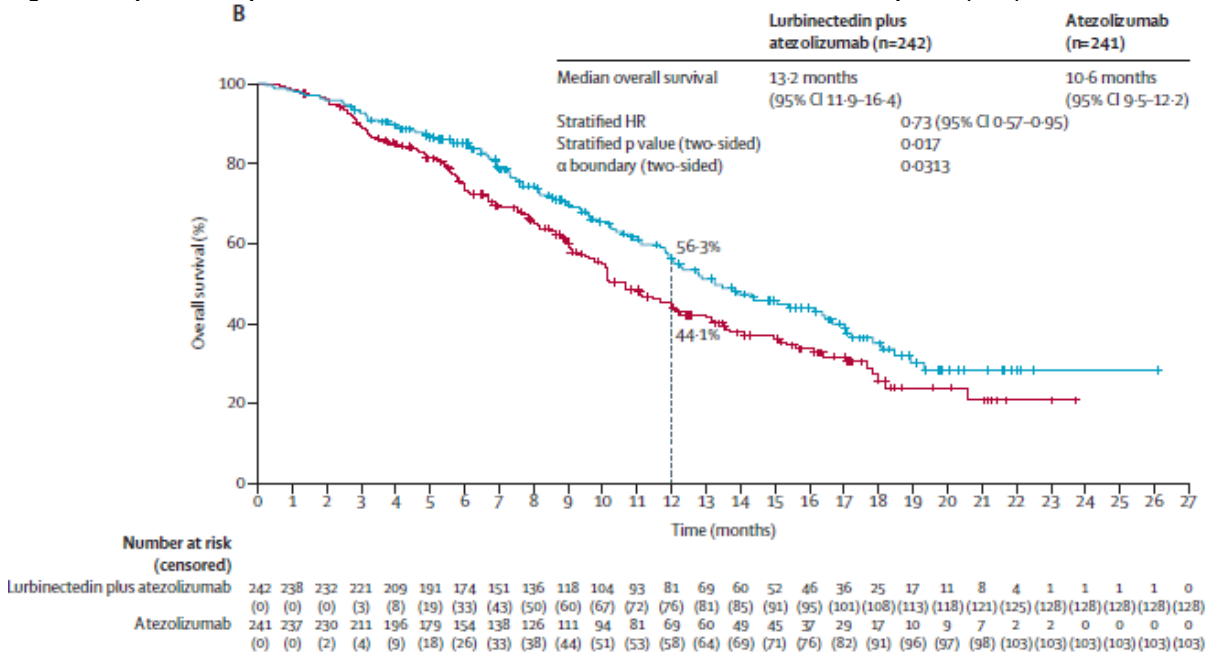
6.17 Table 4 and Figure 1 summarise the results for the IMforte maintenance phase interim analysis for the primary outcome of overall survival and secondary outcomes of 12 month and 24 month event rates.

Table 4: Time to overall survival in the IMforte trial maintenance phase (interim analysis 29 July 2024; FAS)

	LUR+ATE N=242	ATE N=241
Median follow-up, months (range)	14.78 (0.2-26.1)	15.18 (0.6-23.7)
Deaths, n (%)	113 (46.7%)	136 (56.4%)
Median OS, months (95% CI)	13.24 (11.89, 16.36)	10.64 (9.49, 12.16)
Hazard ratio (95% CI) stratified[a]	**0.73 (0.57, 0.95)**	
Time point analysis at 12 months		
Patients remaining at risk	N=81	N=69
Event free rate, % (95% CI)	56.25 (48.97, 63.53)	44.10 (37.00, 51.21)
Difference in event free rate, % (95% CI)	**12.14 (1.97, 22.31)**	
Time point analysis at 24 Months		
Patients remaining at risk	N=1	N=0
Event free rate, % (95%, CI)	28.32 (19.28, 37.36)	NE
Difference in event free rate, % (95%, CI)	NE	

Source: Table 38, p83 of the submission.
Abbreviations: ATE, atezolizumab; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; LDH, lactate dehydrogenase; LUR, lurbinectedin; NE, not estimable; OS, overall survival; PCI, prophylactic cranial irradiation; PS, performance status; ULN, upper limit of normal.
Note: Statistically significant results in bold.
a Stratification factors are ECOG PS at randomisation (0 vs 1, LDH at randomisation (≤ ULN vs > ULN) via laboratory test, presence of liver metastases at enrolment (yes vs no), prior receipt of PCI (yes vs no)

Figure 1: Kaplan Meier plot of interim overall survival in the IMforte trial maintenance phase (FAS)



Source: Figure 7, p84 of the submission.
Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; OS, overall survival.

6.18 Based on a median follow-up of 14.78 months in the lurbinectedin plus atezolizumab arm and 15.18 months in the atezolizumab arm, patients in the lurbinectedin plus atezolizumab arm demonstrated statistically significantly longer median overall survival (13.24 months) compared to the atezolizumab arm (10.64 months; stratified HR = 0.73; 95% CI: 0.57, 0.95). Results based on the unstratified analysis were consistent with the stratified analysis (HR = 0.74; 95% CI: 0.58, 0.96).

6.19 Table 5 and Figure 2 summarise the results for the IMforte maintenance phase analysis for the primary outcome of independent review facility (IRF) assessed progression free survival, and event rates at 6 and 12 months.

Table 5: Time to PFS in the IMforte trial maintenance phase (FAS)

	LUR+ATE N=242	**ATE N=241**
Median follow-up, months (range)	14.78 (0.2-26.1)	15.18 (0.6-23.7)
PFS events, n (%)	174 (71.9%)	202 (83.8%)
Death	31 (12.8%)	19 (7.9%)
Disease Progression	143 (59.1%)	183 (75.9%)
Median PFS, months (95% CI)	5.36 (4.24, 5.75)	2.14 (1.64, 2.73)
Hazard ratio (95% CI) stratified[a]	**0.54 (0.43, 0.67)**	
Time point analysis at 6 months		
Patients remaining at risk	N=76	N=34
Event free rate, % (95% CI)	41.22 (34.58, 47.86)	18.66 (13.45, 23.87)
Difference in event free rate, % (95% CI)	**22.56 (14.12, 31.00)**	
Time point analysis at 12 Months		
Patients remaining at risk	N=24	N=13
Event free rate, % (95%, CI)	20.54 (14.37, 26.72)	12.03 (7.27, 16.80)
Difference in event free rate, % (95%, CI)	**8.51 (0.72, 16.31)**	

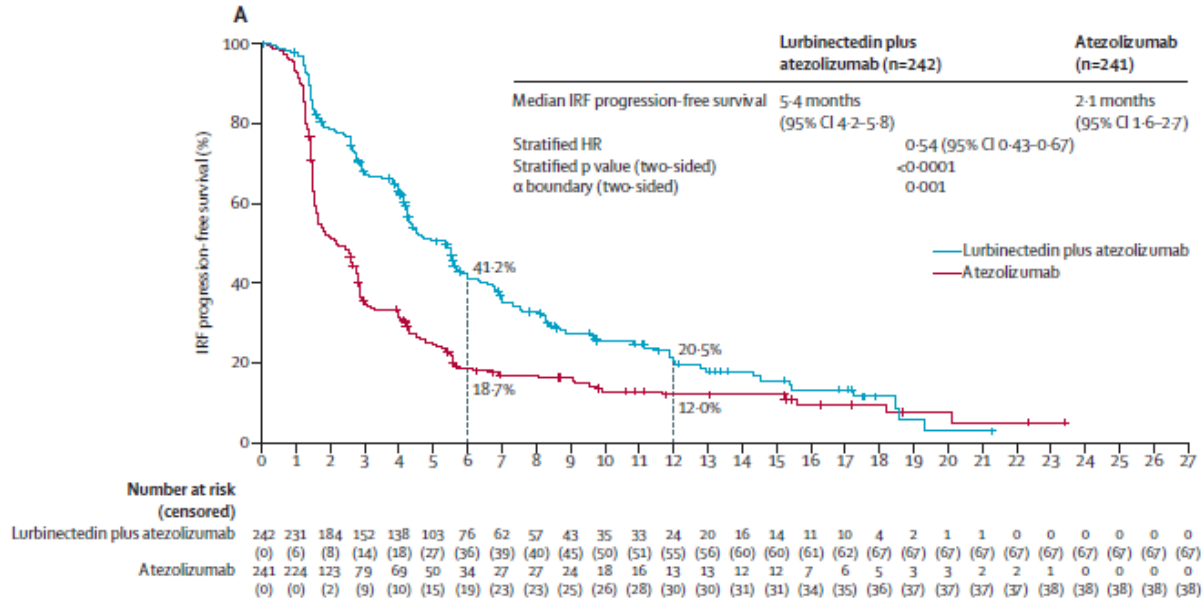
Source: Table 39, p85 of the submission.

Abbreviations: ATE, atezolizumab; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IRF, independent review facility; LDH, lactate dehydrogenase; LUR, lurbinectedin; PCI, prophylactic cranial irradiation; PFS, progression-free survival; PS, performance status; ULN, upper limit of normal.

Note: Statistically significant results in bold.

a Stratification factors are ECOG PS at randomisation (0 vs 1, LDH at randomisation (≤ ULN vs > ULN) via laboratory test, presence of liver metastases at enrolment (yes vs no), prior receipt of PCI (yes vs no)

Figure 2: Kaplan Meier plot of interim progression free survival in the IMforte trial maintenance phase (IRF; FAS)



Source: Figure 8, p86 of the submission.
Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRF, independent review facility; PFS, progression free survival.

6.20 Based on a median follow-up of 14.78 months in the lurbinectedin plus atezolizumab arm and 15.18 months in the atezolizumab arm, patients in the lurbinectedin plus atezolizumab arm demonstrated statistically significantly longer median progression-free survival (5.36 months) compared to the atezolizumab arm (2.14 months; stratified HR = 0.54; 95% CI: 0.43, 0.67). Results based on the unstratified analysis (HR = 0.56; 95% CI: 0.46, 0.69) and with progression free survival assessed by on-site investigators (stratified HR = 0.55; 95% CI: 0.45, 0.66) were consistent with the main analysis.

6.21 Subgroup analyses were conducted by baseline demographic and disease criteria, including age (<65, ≥65 years), sex (male, female), tobacco use (never, prior, current), liver metastases (yes, no), prior prophylactic cranial irradiation (yes, no), ECOG performance status (0, 1), lactate dehydrogenase status (<ULN, ≥ULN) and response to induction therapy (CR, PR, stable disease, progressive disease), for overall survival and progression free survival. Most subgroups demonstrated a consistent trend in overall survival and progression free survival, favouring patients in the lurbinectedin plus atezolizumab arm. However, results indicated that patients with lactate dehydrogenase above the upper limit of normal, with an ECOG performance status of 0, or with prior prophylactic cranial irradiation at maintenance baseline appeared to obtain a smaller benefit with lurbinectedin plus atezolizumab versus atezolizumab. No treatment effect interaction testing was performed.

6.22 Results for the secondary outcome of IRF-assessed confirmed objective response rate (CORR), in patients with measurable disease at randomisation, showed statistically significantly larger proportions of patients treated with lurbinectedin plus atezolizumab achieved confirmed objective response (19.4%) compared to atezolizumab monotherapy (10.4%; risk difference = 8.99; 95% CI: 1.07, 16.90). However, the investigator-assessed analysis did not reach statistical significance (risk difference = 3.90; 95% CI: -3.51, 11.32).

6.23 Quality of life, measured using the EORTC QLQ-C30, suggested that patients were functioning at moderately high levels, with minimal to moderate symptom burden at baseline. Mean EORTC QLQ-C30 scores remained similar at Cycle 6 Day 1 for the lurbinectedin plus atezolizumab and atezolizumab monotherapy arms, and results were generally consistent between treatment arms.

6.24 Other patient relevant outcomes (EORTC QLQ-LC13, EORTC IL46) were generally consistent with EORTC QLQ-C30 scores, with patients remaining stable with no or small differences between treatment arms.

Comparative harms

6.25 Table 6 summarises the key adverse events reported in the IMforte trial maintenance phase.

Table 6: Summary of key adverse events in the IMforte trial maintenance phase (SAS)

	LUR+ATE N=242	ATE N=240
Any adverse event, n (%)	235 (97.1%)	194 (80.5%)
Any adverse event Grade 3-4, n (%)	92 (38.0%)	53 (22.0%)
Serious adverse events, n (%)	75 (31.0%)	41 (17.0%)
Treatment related adverse events, n (%)	202 (83.5%)	96 (40.0%)
Treatment related adverse event Grade 3-4, n (%)	62 (25.6%)	14 (5.8%)
Treatment related serious adverse events, n (%)	28 (11.6%)	9 (3.8%)
AE leading to treatment withdrawal/discontinuation, n (%)	15 (6.2%)	8 (3.3%)
AE leading to any dose modification/interruption, n (%)	92 (38.0%)	33 (13.8%)
Deaths (any adverse events Grade 5), n (%)	12 (5.0%)	6 (2.5%)

Source: Table 52, p103 of the submission.
Abbreviations: AE, adverse event; ATE, atezolizumab; LUR, lurbinectedin; SAS, safety analysis set.

6.26 The ESC noted that there was a higher incidence in the lurbinectedin plus atezolizumab treatment arm of any adverse event, Grade 3–4 adverse event, serious adverse event, treatment related adverse event and adverse events leading to treatment discontinuation or dose modification/interruption, compared to atezolizumab monotherapy. The incidence of grade 5 adverse events (deaths) was also higher in the lurbinectedin plus atezolizumab treatment arm compared to atezolizumab monotherapy. Of the 3 deaths considered treatment related by investigators, 2 were related to lurbinectedin (sepsis and febrile neutropenia), and one was related to atezolizumab monotherapy (sepsis).

6.27 The submission suggested that the addition of lurbinectedin to atezolizumab, and longer treatment exposure in the lurbinectedin plus atezolizumab treatment arm compared to atezolizumab (4.2 months vs 2.1 months), explained some of higher incidence of adverse events associated with lurbinectedin plus atezolizumab.

6.28 The most frequently reported adverse events in the IMforte trial maintenance phase in patients treated with lurbinectedin plus atezolizumab were nausea (36.4%), anaemia (31.8%), fatigue (20.2%), decreased appetite (16.9%), and decreased platelet count (15.3%). Common adverse events reported by >5% of patients treated with atezolizumab only included fatigue (7.9%), diarrhoea (7.5%), anaemia (6.7%), and decreased appetite (6.7%). The ESC noted that patients treated with lurbinectedin should also receive G-CSF prophylaxis and anti-emetics to manage side effects.

Benefits/harms

6.29 On the basis of direct evidence presented in the submission, for every 100 patients treated with lurbinectedin plus atezolizumab in comparison to atezolizumab monotherapy over a median duration of follow-up 14.78 months:

- Approximately 12 additional patients would remain alive at 12 months.
- Approximately 9 additional patients would remain progression free at 12 months.
- Approximately 16 additional patients would experience Grade 3-4 adverse events.
- Approximately 14 additional patients would experience a serious adverse event.

Clinical claim

6.30 The submission described lurbinectedin plus atezolizumab as superior in terms of efficacy and inferior in terms of safety, compared to atezolizumab, as maintenance therapy in patients with ES-SCLC that has not progressed on or after first-line induction therapy with atezolizumab, a platinum-based antineoplastic drug, and etoposide.

6.31 The evaluation noted the following issues for consideration:

- The IMforte trial interim overall survival data were immature, and the magnitude of the benefit experienced by patients treated with lurbinectedin plus atezolizumab may change with longer follow-up.
- The results of the IMforte trial may not be applicable to the Australian setting given the patients randomised into the maintenance treatment phase of the trial were required to have ECOG PS 0-1 and were excluded from the trial if they had CNS metastases, which were inconsistent with the requested restriction. In addition, the impact of baseline differences between the IMforte trial lurbinectedin plus atezolizumab arm and the atezolizumab arm, in measures of disease progression (tumour size T4: 50.8% vs 58.8%; metastases M1c: 47.5%; 58.9%), is unknown. The ESC also noted that the IMforte trial consisted of a relatively young population (median age 66 years) compared to the median age of SCLC diagnosis in Australia (69 years).

6.32 Overall, the ESC noted lurbinectedin plus atezolizumab resulted in a statistically significant survival benefit over atezolizumab monotherapy in patients without CNS metastases. However, the ESC noted that the median survival benefit was small (2.6 months) and lurbinectedin plus atezolizumab was associated with more adverse events than atezolizumab monotherapy.

6.33 The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data.

6.34 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.35 The submission presented a stepped economic evaluation of lurbinectedin plus atezolizumab versus atezolizumab monotherapy as first-line maintenance treatment of ES-SCLC for patients who have not progressed following first-line induction therapy with atezolizumab, carboplatin and etoposide. The economic evaluation was based on the results of the IMforte trial, with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

6.36

6.37 **Table 7** summarises the key components of the economic evaluation.

Table 7: Key components of the economic evaluation

Component	Summary
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Treatments	Lurbinectedin plus atezolizumab versus atezolizumab monotherapy
Outcomes	Progression free life years; life years; quality adjusted life years
Time horizon	7.5 years in the model base case versus a median follow-up of 14.95 months in the IMforte trial. This was truncated to 5 years in the pre-PBAC response.
Cycle length	One week
Methods used to generate results	Partitioned survival analysis
Health states	Progression free; progressed disease; dead
Allocation to health states	The proportions of patients who were progression free, progressed and dead were informed by modelled overall survival (OS) and progression free survival (PFS) curves. Kaplan-Meier estimates for OS and PFS were derived from the IMforte trial and were used directly in the model up to 14.95 months (based on the median duration of follow-up), then extrapolated over the model time horizon using standard parametric functions (OS was extrapolated using a loglogistic function for each treatment arm; PFS was extrapolated using a lognormal function for each treatment arm; non-proportional hazards were justified in the submission). Sensitivity analyses assess the impact of including risk convergence and curve convergence. See discussion in Table 8, 'Overall survival extrapolation' section for further discussion on the extrapolations. Adjustments were included in the model to ensure that PFS did not exceed OS in any cycle, and that the progression-free and overall survival event risks in each cycle were no lower than the risk of death in the age- and sex-matched Australian population, based on ABS life tables. These adjustments do not affect model results in the base case, as PFS did not exceed OS, and event risks remained higher than general population mortality over the model time horizon. Time on maintenance treatment was based on trial-based estimates of the mean number of cycles of therapy, which were not extrapolated beyond the duration of the trial.

Component	Summary
Utility values	Health state utilities were derived from alternative utilities used in a sensitivity analysis in the July 2019 atezolizumab submission, derived from EQ-5D-5L data from the atezolizumab IMpower133 trial (progression-free 0.72; progressed disease 0.70). Sensitivity analyses explored the impact of using EORTC QLQ-C30 data from the IMforte trial mapped to EQ-5D-3L using the Longworth 2014 algorithm (progression-free 0.706; progressed disease 0.675); and health state utilities commonly used in published economic evaluations (Nafees 2008, Yang 2019, Shen 2018). The ESC noted that utility values applied in the base case to the progression-free and progressed health states from the IMpower133 trial were very similar. 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 the IMpower133 trial. The QALY loss associated with adverse events in each arm was based on serious adverse events with an incidence of at least 2% of patients in any treatment arm (pneumonia, respiratory tract infection, dyspnoea, decreased platelet count), disutilities from Sullivan 2011, and an implied duration of each serious adverse event of one year. See paragraph 6.45 for further detail.
Costs	Lurbinectedin treatment costs were based on the dosing regimen in the IMforte trial (consistent with the draft lurbinectedin Product Information), the distribution of 2 mg vials required per dose based on body surface area data from the IMforte trial, the proposed effective price, and the mean number of lurbinectedin doses in the IMforte trial. The ESC noted that the estimated costs for lurbinectedin were based on the 2 mg vial only. The pre-PBAC response reduced the EMP of the 2 mg vial from $[redacted] to $[redacted]. Atezolizumab treatment costs were based on the dosing regimen in the atezolizumab Product Information, an effective price based on the assumption of a 75% rebate, and the mean number of atezolizumab doses in each arm of the IMforte trial. See discussion in Table 8, 'Overall survival extrapolation' section for further discussion on treatment costs. Administration costs were based on MBS Item 13950 and the mean number of doses administered in the IMforte trial. Concomitant therapy costs associated with G-CSF prophylaxis were based on the use of filgrastim assuming one administration per lurbinectedin treatment cycle. Adverse event costs were based on serious adverse events with an incidence of at least 2% in either treatment arm of the IMforte trial, and 2019-2020 NHCDC admitted acute cost weights for AR-DRG Version 10.0, assuming minor complexity only. The ESC noted that costs of adverse events did not account for patients experiencing more than one adverse event. Further, only hospital costs for minor complexity are included, instead of weighted minor/major complexity. Costs associated with subsequent therapies were based on the proportion of patients receiving subsequent anti-cancer therapies in the IMforte trial, with the costs of carboplatin plus etoposide, based on the eviQ protocol, used as a proxy for all therapies. Administration costs were included based on MBS Item 13950. The costs associated with subsequent radiotherapy or surgery were not included. Health state costs were based on the frequency of CT scans and MRIs recommended in the NCCN (2025) and ESMO (Dingemans 2021) guidelines (applied to patients in the progression-free state only) and the assumption that all patients would require a specialist consultation every 4 weeks. Unit costs were based on MBS items 105, 56301 and 63001. Terminal care costs associated with lung cancer death were derived from the AIHW 'The last year of life: patterns in health service use and expenditure' dataset. It was assumed that there would be no costs associated with other deaths. The proportions of deaths due to lung cancer were based on deaths due to disease progression in the IMforte trial.
Discounting	5% per year applied to costs and outcomes
Software package	Excel 2021

Source: Sections 3.3 to 3.6, pp148-177 of the submission.
Abbreviations: ABS, Australian Bureau of Statistics; AIHW, Australian Institute of Health and Welfare; AR-DRG, Australian Refined Diagnosis Related Group; CT, computed tomography; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; ESMO, European Society for Medical Oncology; G-CSF, granulocyte colony stimulating factor; MBS, Medicare Benefits Schedule; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NHCDC, National Hospital Cost Data Collection; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year.

6.38 The economic model utilised a partitioned survival analysis with 3 mutually exclusive health states of progression free, progressed disease, and dead, based on extrapolated progression free survival and overall survival curves from the lurbinectedin plus atezolizumab and atezolizumab monotherapy arms of the IMforte trial over a 7.5-year time horizon. The PBAC previously considered a time horizon of 5 years appropriate for atezolizumab for ES-SCLC and based on the uncertain magnitude of overall survival benefit, recommended that overall survival curves should converge between 2 and 5 years (paragraph 7.12, atezolizumab PSD, July 2019 PBAC meeting). The pre-PBAC response reduced the time horizon to 5 years. The lurbinectedin model does not incorporate convergence in the base case but explored the impact of convergence in sensitivity analyses.

6.39 Key drivers of the economic model are summarised in Table 8.

Table 8: Key drivers of the model

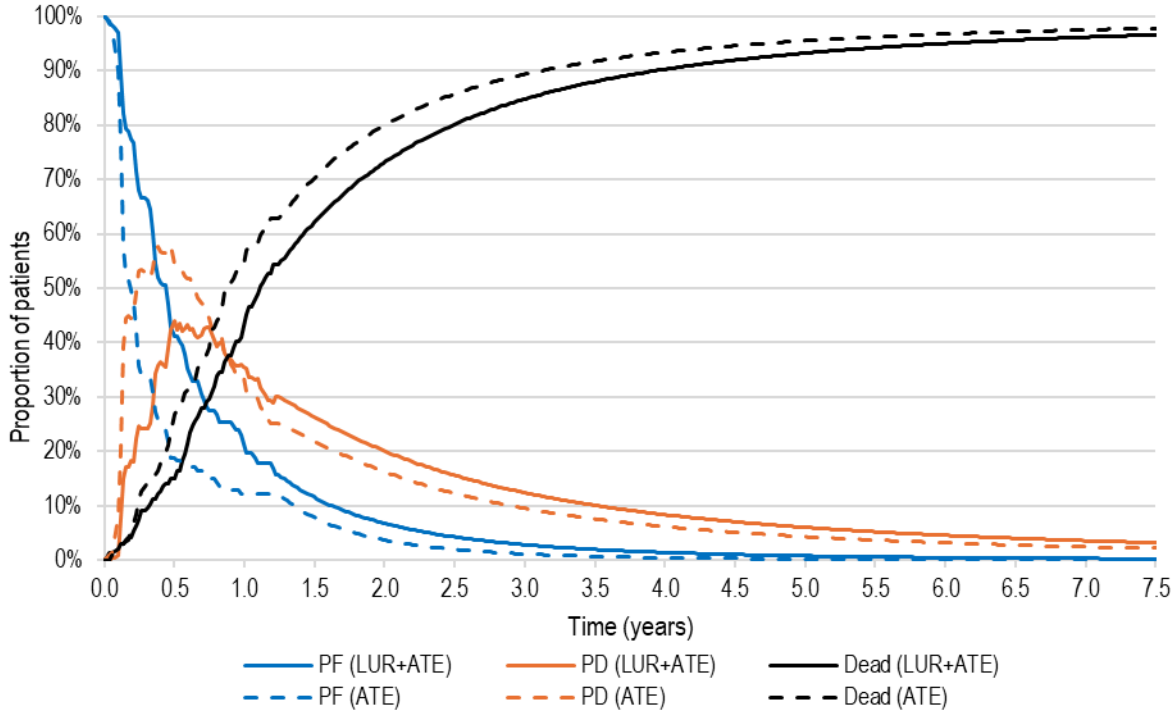
Description	Method/Value	Impact
Overall survival extrapolation	The Kaplan Meier overall survival curve for each treatment arm from the IMforte trial was used up to cycle 66 of the model (14.95 months). The point of extrapolation was based on the median duration of follow-up of the IMforte trial. An assessment of data maturity conducted in the submission using the Gebzki 2018 criteria indicated that Kaplan Meier data remained reliable over 19.5 to 21.7 months. Sensitivity analyses indicated that the model was sensitive to extending the point of extrapolation to the lower bound of reliability (19.5 months in the lurbinectedin plus atezolizumab arm; 19.8 months in the atezolizumab arm). In the base case, overall survival curves were extrapolated using independently derived loglogistic functions for each treatment arm. The submission claimed that the loglogistic function was the most suitable based on goodness of fit statistics (AIC and BIC), visual inspection, and comparison of survival estimates to estimates from long-term studies. The submission claimed that the generalised gamma, Gompertz and Weibull functions were overly pessimistic, based on comparisons with long-term studies. Data from long-term follow-up of the durvalumab CASPIAN trial (Paz-Arez 2022) demonstrated 3-year survival of 17.6% and data from the extension study of the atezolizumab IMpower133 trial (Reck 2024) demonstrated 3-year survival of 16% and 5-year survival of 12%. All of the extrapolation functions appeared to underestimate overall survival in the atezolizumab arm, based on the longer-term follow-up data. In the base case of the model, 10.7% of patients in the atezolizumab arm remain alive at 3 years, and 4.5% of patients remain alive at 5 years, suggesting that the model substantially underestimates survival in the atezolizumab arm. The PSCR stated that the CASPIAN and IMpower133 trials were both induction plus maintenance trials, whereas the IMforte trial is exclusively a maintenance trial, meaning the comparison of modelled overall survival is misleading. The ESC noted that based on statistical fit (AIC/BIC), the best fitting functions were the Weibull function for the lurbinectedin plus atezolizumab arm and the loglogistic function for the atezolizumab only arm. The ESC noted that both functions appeared to be a reasonable fit for the available overall survival data, and that the model was sensitive to this choice. The submission assumed that there would be no convergence in extrapolated overall survival in the base case analysis. This was a strong assumption in favour of lurbinectedin and was inconsistent with previous PBAC recommendations to include curve convergence when considering atezolizumab for ES-SCLC (paragraph 7.12, atezolizumab PSD, July 2019 PBAC meeting). See paragraphs 6.38 and 6.41 to 6.43 for further discussion.	High, favours lurbinectedin

Description	Method/Value	Impact
Duration of maintenance treatment	The duration of treatment in the economic model was based on the average number of treatment cycles from the IMforte trial at the July 2024 data cut. The model will underestimate the average duration of treatment, given 18.6% of patients in the lurbinectedin plus atezolizumab arm and 13.3% of patients in the atezolizumab arm remained on treatment at the data cut-off; and the data were not extrapolated beyond the trial, which was inconsistent with the approach used for progression-free and overall survival. Although Kaplan Meier time of treatment data were not available, the PSCR stated that the progression-free survival data indicated that less than 20.54% of patients remain alive and progression-free beyond 12 months, decreasing to less than 5% beyond 20 months. Further, the PSCR noted that 86% of lurbinectedin discontinuations were due to disease progression or death and only 7.9% of lurbinectedin patients received more than 12 months of treatment in the trial. Therefore, on balance, the PSCR stated that mean exposure over the trial period is considered a reasonable estimate of expected exposure to lurbinectedin in clinical practice. Sensitivity analyses indicated that the model was sensitive to alternative estimates of treatment duration, using modelled progression-free survival as a proxy for treatment duration.	High, favours lurbinectedin

Source: Constructed during the evaluation.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ES-SCLC, extensive stage small cell lung cancer; PSD, Public Summary Document.

6.40 Figure 3 presents model traces for the lurbinectedin plus atezolizumab and atezolizumab arms of the economic model.

Figure 3: Model traces for lurbinectedin plus atezolizumab and atezolizumab arms of the economic model



Source: Figure 26B, p178 of the submission.
Abbreviations: ATE, atezolizumab; LUR, lurbinectedin; PD, progressed disease; PF, progression free.

6.41 The model traces show a survival benefit for lurbinectedin plus atezolizumab compared to atezolizumab that persists over the 7.5 year time horizon of the model. Mortality is higher in the lurbinectedin plus atezolizumab arm compared to the atezolizumab arm in 7 of the first 9 weekly cycles, after which mortality is lower in the lurbinectedin plus atezolizumab arm. The peak difference in mortality occurs after 10.8 months (13.5%; 37.7% versus 51.2%), after which the curves begin to converge over time. The proportions of patients remaining alive in the lurbinectedin plus atezolizumab arm at 5 and 7.5 years were 6.8% and 3.4%, respectively, compared to 4.5% and 2.2% in the atezolizumab arm. The PSCR stated that the 7.5-year model base case was chosen to adequately capture the lifetime impact of improved survival outcomes with lurbinectedin, and survival outcomes effectively converged without manual application of convergence over this period (only a 1.2% difference in OS at 7.5 years).

6.42 The traces also show a difference in progression-free survival, in favour of lurbinectedin plus atezolizumab compared to atezolizumab. The progression-free traces separate from the first model cycle, with a peak difference at 3.4 months (33.1%; 66.7% versus 33.5%) after which the curves slowly converge over time. The PSCR stated that maintaining more patients progression-free for longer was likely indicative of a more durable survival benefit.

6.43 Noting the comments above, the PSCR stated that applying the same constraints, with regard to the time horizon and convergence, as were applied to atezolizumab was likely to bias the results against lurbinectedin. The ESC, noting the small survival benefit associated with lurbinectedin and the applicability issues associated with the trial population, considered that a 5-year time horizon with convergence applied as per the atezolizumab model would be appropriate.

6.44 A smaller proportion of patients were in the progressed disease state in the lurbinectedin plus atezolizumab arm compared to the atezolizumab arm until 10.6 months, when a higher proportion of lurbinectedin plus atezolizumab patients have progressed disease (due to longer survival).

6.45 The ESC considered that the submission's approach to the inclusion of adverse events in the economic model, based on serious adverse events with an incidence of at least 2% of patients in any treatment arm only, underestimated the impact of lurbinectedin-related adverse events. The submission's approach excluded gastrointestinal (nausea, decreased appetite, diarrhoea, vomiting, constipation) and haematological (anaemia, fatigue, thrombocytopaenia, decreased neutrophil count, neutropenia) adverse events associated with lurbinectedin treatment, which may be associated with costs and quality of life implications. The use of adverse event incidence will underestimate the costs associated with adverse events, as it does not account for patients who experience more than one adverse event (adverse event rates were not reported in the IMforte trial report).

6.46 The results of the stepped economic evaluation are presented in Table 9. Results were based on the assumed effective price of atezolizumab. The results of a revised base

case presented in the pre-PBAC response, which reduced the time horizon from 7.5 to 5 years and the price of the 2 mg vial (which the economic model was based on) from $845 to $485, is also presented.

Table 9: Results of the stepped economic evaluation

Step and component	Lurbinectedin + atezolizumab	Atezolizumab	Increment
Step 1: Modelled analysis over 15 months (median duration of follow-up of the IMforte trial) including maintenance drug and administration costs; based on progression free life years and life years as the outcome; costs and outcomes discounted.			
Costs	$[redacted]	$11,834	$[redacted]
Progression free life years	0.5513	0.3539	0.1974
Life years	0.9383	0.8460	0.0923
Incremental cost per progression free life year gained			$[redacted][1]
Incremental cost per life year gained			$[redacted][2]
Step 2: As for Step 1, with outcomes based on QALYs			
Costs	$[redacted]	$11,834	$[redacted]
QALYs	0.6622	0.5956	0.0665
Incremental cost per QALY gained			$[redacted][3]
Step 3: As for Step 2, extrapolated to 7.5 years			
Costs	$[redacted]	$11,834	$[redacted]
Life years	1.6296	1.3454	0.2843
QALYs	1.1491	0.9468	0.2023
Incremental cost per life year gained			$[redacted][4]
Incremental cost per QALY gained			$[redacted][1]
Step 4: As for Step 3, with the inclusion of other health care resource use (costs associated with concomitant medicines, subsequent systemic treatments, health states, and terminal care).			
Costs	$[redacted]	$40,616	$[redacted]
Life years	1.6296	1.3454	0.2843
QALYs	1.1491	0.9468	0.2023
Incremental cost per life year gained			$[redacted][4]
Incremental cost per QALY gained			**$**[redacted][1]
Pre-PBAC response updated base case (time horizon = 5 years; 2 mg vial = $[redacted])			
Costs	$[redacted]	$40,166	$[redacted]
QALYs	1.085	0.905	0.180
Incremental cost per QALY gained			**$**[redacted][5]

Source: Table 104, p181 of the submission; 'Zepzelca_SCLC-CUA' model spreadsheet provided with the submission.
Abbreviations: QALY, quality adjusted life year.
Note: Atezolizumab costs were based on the published AEMP and an assumed 75% rebate to account for the special pricing arrangement and risk sharing arrangement.
The redacted values correspond to the following ranges:
[1] *$135,000 to < $155,000*
[2] *$255,000 to < $355,000*
[3] *$355,000 to < $455,000*
[4] *$95,000 to < $115,000*
[5] *$75,000 to < $95,000*

6.47 Based on the economic model, treatment with lurbinectedin plus atezolizumab was associated with an incremental cost per QALY gained of $115,000 to < $135,000 compared with atezolizumab alone. Extrapolation of the time horizon to 7.5 years had the largest impact on the stepped economic evaluation.

6.48 The difference in total cost between treatment arms was primarily driven by drug costs for lurbinectedin plus atezolizumab, which were partially offset by terminal care costs. The ESC considered that there was likely to be substantial double counting of MBS services included in terminal care costs, as these were explicitly captured in health state costs in the economic model.

6.49 The difference in health outcomes between treatment arms was primarily driven by the improved survival of patients in the lurbinectedin plus atezolizumab arm compared to the atezolizumab arm.

6.50 In the model, 67% of the incremental QALYs and 4% of the incremental costs were accrued in the extrapolated period beyond 15 months.

6.51 For every patient treated with lurbinectedin plus atezolizumab versus atezolizumab alone and followed up for 7.5 years, the economic model (without discounting) estimated that there would be:

- An additional 3.8 months of life lived.
- An additional 3.3 months spent progression-free.
- Additional maintenance therapy and administration costs (including concomitant therapy) of $28,750.
- Reduced subsequent therapy costs of $267 and reduced terminal care costs of $2,068.
- Additional health state costs of $821 and additional adverse event costs of $223.

6.52 The submission acknowledged that the ICER was higher compared to previous PBAC decision making for cancer therapies, and stated that it should be considered in the context of the aggressive nature of ES-SCLC, and the magnitude of benefit associated with lurbinectedin treatment (an increase in median overall survival in the IMforte trial from 10.64 months to 13.24 months) which was based on high quality evidence from a head-to-head randomised trial. The submission also noted that the sponsor would be willing to discuss entering a risk sharing arrangement (RSA) to help mitigate uncertainty around the cost-effectiveness of lurbinectedin, noting that an arrangement was recommended by the PBAC for listing atezolizumab based on a fixed number of atezolizumab doses that was shorter than the estimated average treatment duration.

6.53 The PBAC recommended listing of atezolizumab for induction and maintenance treatment of ES-SCLC at the November 2019 meeting. The PBAC was satisfied that the proposal to achieve cost-effectiveness through RSA rebates, in addition to a proposed reduction in the effective price, was reasonable (paragraph 6.1, atezolizumab PSD, November 2019 PBAC meeting). The PBAC considered the cost-effectiveness of atezolizumab was acceptable at the price applied in the economic model, which resulted in an ICER of $45,000 to $75,000 per QALY gained (paragraph 6.8, atezolizumab PSD, November 2019 PBAC meeting).

6.54 The results of key sensitivity analyses presented in the submission and conducted during the evaluation are summarised in Table 10.

Table 10: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALYs	ICER	% change
Base case	**$[redacted]**	**0.2023**	**$[redacted][1]**	**-**
Discount rate (base case: 5% costs and outcomes)				
0% costs and outcomes	$[redacted]	0.2229	$[redacted][1]	-[redacted]%
3.5% costs and outcomes	$[redacted]	0.2080	$[redacted][1]	-[redacted]%
Time horizon (base case 7.5 years)				
5 years	$[redacted]	0.1801	$[redacted][2]	+[redacted]%
Overall survival extrapolation (base case: modelled independently, using a loglogistic function for each arm)				
Both arms modelled independently: lognormal	$[redacted]	0.2839	$[redacted][3]	-[redacted]%
Both arms modelled independently: Weibull	$[redacted]	0.1526	$[redacted][4]	+[redacted]%
Estimated modelled jointly: Weibull	$[redacted]	0.1640	$[redacted][4]	+[redacted]%
Progression-free survival extrapolation (base case: modelled independently, using a lognormal function for each arm)				
No difference in PFS between arms beyond median duration of follow-up	$[redacted]	0.2009	$[redacted][2]	[redacted]%
Extrapolation assumptions (base case: no convergence applied to PFS and OS curves)				
Risk convergence of OS and PFS from 2 years	$[redacted]	0.1802	$[redacted][2]	+[redacted]%
Risk convergence OS and PFS from 5 years	$[redacted]	0.2014	$[redacted][2]	+[redacted]%
5 year time horizon and OS curve convergence from 2 to 5 years[a]	$[redacted]	0.1690	$[redacted][4]	+[redacted]%
Point of extrapolation for parametric functions (base case: median follow-up of 14.95 months from the IMforte trial)				
Gebski criterion 1 (2.5%)[b]	$[redacted]	0.1662	$[redacted][4]	+[redacted]%
Time on maintenance therapy (base case: based on the mean number of doses/cycles in the IMforte trial: LUR 8.1; ATE in combination with LUR 8.2; ATE monotherapy 6.1)				
Using modelled PFS as a proxy for time on treatment (8.95 cycles for LUR and ATE as combination; 5.49 cycles for ATE monotherapy)	$[redacted]	0.2023	$[redacted][4]	+[redacted]%
Using additional PFS in the extrapolated period (beyond 14.95 months) to derive the additional cycles of therapy beyond the trial (8.1+2.02 cycles for LUR; 8.2+2.02 cycles for ATE as combination; 6.1+1.04 cycles for ATE monotherapy)	$[redacted]	0.2023	$[redacted][4]	+[redacted]%
Health state utilities (base case: derived from the IMpower133 atezolizumab trial, reported in the July 2019 atezolizumab PSD; progression free 0.720; progressed disease 0.700)				
IMforte EORTC QLQ-C30 data mapped to EQ-5D-3L: PF 0.706; PD 0.675	$[redacted]	0.1981	$[redacted][2]	+[redacted]%
Lurbinectedin maintenance treatment costs (base case: based on use of 2 mg lurbinectedin vials only)				
Lurbinectedin costs based on 4 mg vials only	$[redacted]	0.2023	$[redacted][2]	+[redacted]%
Terminal care costs (base case: based on lung cancer death costs in the last year of life from AIHW data, with prescription costs removed; applied to the proportion of deaths due to disease progression (79.6% for lurbinectedin plus atezolizumab patients, 86.7% for atezolizumab monotherapy patients, $26,408)				
Terminal care costs excluded	$[redacted]	0.2023	$[redacted][2]	+[redacted]%
Multivariate sensitivity analyses				
Time horizon = 5 years; Convergence from Years 2 to 5; Extrapolation based on Gebski criterion 1 (2.5%)	$[redacted]	0.140	$[redacted][4]	+[redacted]%
Time horizon = 5 years; Convergence from Years 2 to 5; Extrapolation based on Gebski criterion 1 (2.5%); Removal of terminal care costs	$[redacted]	0.140	$[redacted][4]	+[redacted]%
Time horizon = 5 years; Convergence from Years 2 to 5;	$[redacted]	0.140	$[redacted][4]	+[redacted]%

Analyses	Incremental cost	Incremental QALYs	ICER	% change
Base case	**$[redacted]**	**0.2023**	**$[redacted][1]**	**-**
Extrapolation based on Gebski criterion 1 (2.5%); Removal of terminal care costs; 4 mg vials only				

Source: Tables 108-111, pp184-186 of the submission; 'Zepzelca_SCLC-CUA' model spreadsheet provided with the submission.
Abbreviations: ATE, atezolizumab; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; ES-SCLC, extensive stage small cell lung cancer; ICER, incremental cost-effectiveness ratio; LUR, lurbinectedin; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; PSD, Public Summary Document; QALY, quality adjusted life year.
Note: Atezolizumab costs were based on the published AEMP and an assumed 75% rebate to account for the special pricing arrangement and risk sharing arrangement.
[a] The PBAC recommended a 5 year time horizon and curve convergence between 2 and 5 years in consideration of the July 2019 atezolizumab submission.
[b] Kaplan Meier data were used up to 19.3 months for LUR+ATE PFS; 20.1 months for ATE PFS; 19.8 months for LUR+ATE OS; 19.5 months for ATE OS.
[c] Kaplan Meier data were used up to 19.3 months for LUR+ATE PFS; 22.3 months for ATE PFS; 21.7 months for LUR+ATE OS; 21.3 months for ATE OS.
[d] Kaplan Meier data were used up to 19.3 months for LUR+ATE PFS; 20.1 months for ATE PFS; 21.7 months for LUR+ATE OS; 21.3 months for ATE OS.
The redacted values correspond to the following ranges:
[1] $115,000 to < $135,000
[2] $135,000 to < $155,000
[3] $95,000 to < $115,000
[4] $155,000 to < $255,000

6.55 Multivariate sensitivity analyses were conducted during the evaluation due to the uncertainty associated with extrapolated overall survival. The multivariate sensitivity analyses demonstrated that the estimated ICER per QALY gained for lurbinectedin plus atezolizumab compared to atezolizumab was highly sensitive to alternative assumptions (point of extrapolation, parametric survival function, risk of convergence and time horizon) regarding the extrapolation of overall survival.

6.56 The ESC considered that a more conservative model would apply a 5-year time horizon and apply convergence in line with the atezolizumab monotherapy model. In addition, the ESC considered that the point of extrapolation should be based on Gebski criterion 1 (2.5% threshold) noting that it represents a valid estimate, particularly given the uncertainty associated with the overall survival extrapolation. When combined with the extrapolation of overall survival estimated independently and applying the loglogistic function for each arm (as used in the submissions base case), the ESC noted that the ICER increased to $155,000 to < $255,000 per QALY. The ESC noted that the removal of terminal care costs and using only the 4 mg vial of lurbinectedin further increased the ICER.

Drug cost/patient/course

6.57 Lurbinectedin maintenance treatment costs in the economic evaluation and financial implications were based on use of the 2 mg vial only.

6.58 The cost of lurbinectedin per patient per course, based on the 2 mg vial (assuming 58.5% of patients require 3 vials, 41.4% require 4 vials and 0.1% require 5 vials per dose; for 8.1 doses) was $[redacted] in the economic model and $[redacted] in the financial estimates (with the difference due to a difference in the public/private hospital script distribution).

Table 11: Drug cost per patient for lurbinectedin plus atezolizumab and atezolizumab monotherapy

	Lurbinectedin plus atezolizumab			Atezolizumab monotherapy		
	Trial	**Economic model**	**Financial estimates**	**Trial**	**Economic model**	**Financial estimates**
Mean cycles of treatment	LUR: 8.1[a] ATE: 8.2[b]	LUR: 8.1[a] ATE: 8.2[b]	LUR: 8.1[a] ATE: 8.2[b]	ATE: 6.1[c]	ATE: 6.1[c]	ATE Q3W: 6.1[c] ATE Q4W: 4.575[d] DUR Q4W: 4.575[d]
Average dose per cycle	NR	LUR: 6.83 mg[e] ATE: 1,200 mg[f]	LUR: 6.83 mg[e] ATE: 1,200 mg[f]	NR	ATE: 1,200 mg[f]	ATE Q3W: 1,200–1,875 mg[g] ATE Q4W: 1,680 mg[g] DUR Q4W: 1,500 mg[g]
Cost per dose	-	LUR: $[redacted][h] ATE: $1,814.05[i]	LUR: $[redacted][j] ATE: Public: $1,778.07[k] Private: $1,918.20[k]	-	ATE: $1,814.05[h]	ATE Q3W[k]: Public: $1,778.07 Private: $1,918.20 General: $1,849.77 S100 CT: $1,686.84 ATE Q4W[k]: Public: $2,452.81 Private: $2,630.72 DUR Q4W[k]: Public: $2,781.81 Private: $2,978.14
Cost/patient/ course[l]	-	LUR: $[redacted] ATE: $14,875	LUR: $[redacted] ATE: Public: $14,580 Private: $15,729	-	ATE: $11,066	ATE: $10,290– $12,036 DUR: $12,727– $13,625

Source: Constructed during the evaluation using the economic model and financial estimates in the submission

Abbreviations: AEMP, approved ex-manufacturer price; ATE, atezolizumab; BSA, body surface area; CT, chemotherapy; DPMA, dispensed price for maximum amount; DUR, durvalumab; LUR, lurbinectedin; NR, not reported; PI, Product Information; Q3W, every 3 weeks; Q4W, every 4 weeks; S100, Section 100.

[a] Based on the mean number of lurbinectedin doses from the IMforte trial at the July 2024 data cut.

[b] Based on the mean number of atezolizumab doses from the lurbinectedin + atezolizumab arm of the IMforte trial at the July 2024 data cut.

[c] Based on the mean number of atezolizumab doses from the atezolizumab arm of the IMforte trial at the July 2024 data cut.

[d] Mean cycles of treatment for 4-weekly atezolizumab and durvalumab regimens were assumed to 3/4 of the mean cycles of treatment of the 3-weekly atezolizumab monotherapy regimen from the IMforte trial (=6.1 cycles×21 days/28 days).

[e] Based on the recommended dosing regimen of 3.2 mg/m^2 once every 21 days in the draft lurbinectedin PI. An average dose of 6.83 mg was derived (3.42×2 mg vials), based on BSA data from the IMforte trial (mean 1.83 (SD 0.21), range 1.35-2.63 m^2), and assuming a normal distribution (= 58.5%×3 + 41.4%×4 + 0.1%×5 vials).

[f] Based on dosing regimen of 1,200 mg once every 21 days in the atezolizumab Product Information.

[g] Based on the maximum quantities/amounts listed on the PBS.

[h] Derived from the proposed effective AEMP per dose of $[redacted] (=$[redacted]×3.42 vials), and assuming a 48.1%/51.9% public/private split (based on the distribution of atezolizumab and durvalumab maintenance script use in 2024).

[i] The estimated effective AEMP for atezolizumab ($1,686.84) was derived based on the published AEMP ($6,747.36) and an assumed 75% rebate. The weighted average DPMA ($1,814.05) was derived assuming a 48.1%/51.9% public/private split (based on the distribution of atezolizumab and durvalumab maintenance script use in 2024).

[j] Derived from the proposed effective AEMP per dose of $[redacted] (=$[redacted]×3.42 vials), and assuming a 47.1%/52.9% public/private split (based on the distribution of atezolizumab and durvalumab maintenance script use in 2024).

[k] Based on estimated effective AEMPs per vial assuming a 75% rebate on the published AEMP.

[l] Based on mean number of doses multiplied by the cost per dose.

Estimated PBS usage & financial implications

6.59 This submission was considered by DUSC. The submission used a market share approach to estimate the utilisation and financial impact of listing lurbinectedin plus atezolizumab on the PBS, for ES-SCLC maintenance therapy. The estimates presented in the submission were based on the proposed effective prices of lurbinectedin, and the assumed effective prices of atezolizumab and durvalumab (based on a 75% rebate).

6.60 The submission acknowledged that costs associated with primary prophylaxis with G-CSF and subsequent anti-cancer therapies, included in the modelled economic evaluation, were not included in the financial implications, stating that the costs and cost offsets associated with these treatments are expected to be marginal over the 6-year budget impact analysis period.

6.61 Table 12 presents a summary of the key inputs for the financial estimates.

Table 12: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comments
Eligible population			
Historic ES-SCLC maintenance therapy market	ES-SCLC continuing services (ATE; DUR) 2020: 1,743; 0 2021: 3,591; 0 2022: 4,055; 0 2023: 4,101; 3 2024: 4,379; 191	Based on utilisation of ES-SCLC continuing treatment scripts for atezolizumab (11928T, 11929W, 12076N, 12078Q, 14225Q, 14226R) and durvalumab (13780G 13766M), assuming all regimens (3 weekly and 4 weekly) would be impacted by the listing of lurbinectedin.	-
Market growth rate	1.3% per annum	Based on the annualised growth in the number of incident SCLC cases in Australia (from 1,188 in 2011 to 1,330 in 2020) from AIHW Cancer data in Australia 2024. Applied annually to the number of continuing atezolizumab and durvalumab scripts in 2024 to estimate script numbers in 2025-2031.	The evaluation considered it was unclear whether the growth rate in the number of incident cases of SCLC in Australia would reflect the growth in continuing scripts of atezolizumab and lurbinectedin. The average annual increase in atezolizumab and durvalumab between 2021 and 2024 was 10.1%. The DUSC considered that the market growth rate of 1.3% was reasonable. The DUSC considered the larger growth rate in atezolizumab and durvalumab scripts between 2021 and 2024 could have been use outside of the restriction in patients with early relapsed limited stage-SCLC (LS-SCLC).
Treatment utilisation			
Uptake of lurbinectedin plus atezolizumab	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Assumed. Based on the claimed superior effectiveness of lurbinectedin + atezolizumab compared to atezolizumab monotherapy in ES-SCLC maintenance therapy.	The PSCR noted the most recent version of the National Comprehensive Cancer Network (NCCN) guidelines for small cell lung cancer which includes lurbinectedin + atezolizumab as a preferred primary maintenance therapy for ES-SCLC. The DUSC considered the assumed treatment uptake rate to be reasonable in Years 1-3.

Data	Value	Source	Comments
Mean doses per course of treatment of lurbinectedin, atezolizumab and durvalumab	LUR: 8.1 doses ATE: 8.2 doses ATE mono: 6.1 doses ATE or DUR 4 weekly: 4.58 doses	Lurbinectedin and atezolizumab doses derived from the IMforte trial treatment exposure. Atezolizumab and durvalumab 4 weekly regimen mean doses were assumed to 3/4 of 3 weekly exposure (=21 days/28 days)	As per the economic evaluation, the mean numbers of doses were derived from the IMforte trial at the July 2024 data cutoff, with 18.6% patients in the lurbinectedin plus atezolizumab arm and 13.3% patients in the atezolizumab monotherapy arm still receiving treatment, an underestimate of treatment exposure.
Script equivalence between ES-SCLC maintenance therapies	ATE 3 wkly to LUR: 1.33 (8.1/6.1) ATE/DUR 4 wkly to LUR 1.77 (8.1/4.58) ATE 3 wkly to ATE in combination with LUR 1.34 (8.2/6.1) ATE/DUR 4 wkly to ATE in combination with LUR 1.79 (8.2/4.58)	Calculated based on the mean numbers of doses of lurbinectedin + atezolizumab, and atezolizumab monotherapy administered in the IMforte trial, assuming similar mean numbers of doses of durvalumab and atezolizumab monotherapy.	The DUSC noted this parameter was dependent on the mean doses per course of treatment. The method used to adjust treatment exposure between 3 and 4 weekly regimens appeared reasonable. However, the assumption that the mean number of doses of durvalumab would be the same as for atezolizumab monotherapy was not adequately supported.
Lurbinectedin average dose	Lurbinectedin 6.83 mg (3.42 × 2 mg vials)	Based on the effective EMP per average dose of $[redacted] ($[redacted] × 3.42 × 2 mg vials) assuming a public/private hospital split of 47.1%/52.9% (based on the distribution of atezolizumab and durvalumab maintenance script use in 2024).	The submission requested listing of both 2 mg and 4 mg vials; however, the estimated average dose of lurbinectedin was derived based on 2 mg vials only. The mean BSA derived from the IMforte trial was not reported in the IMforte CSR or key publications (Paz-Ares 2025) and could not be verified. Mean BSA reported in the atezolizumab IMpower133 trial was 1.86 m^2. Dooley 2004, a study of Australian patients presenting for chemotherapy at a Melbourne cancer clinic between 1996 and 2000, estimated a mean BSA 1.80 m^2 when calculating treatment costs for BSA-based dosing regimens. The DUSC considered this parameter to be reasonable but noted the Dooley 2004 study may not reflect current mean BSA given the study was conducted over 20 years ago.
Lurbinectedin weighted average effective price per average dose	Public: $[redacted] Private: $[redacted] weighted average: $[redacted]	Based on the effective EMP per median dose of $[redacted] ($[redacted] × 3.42 vials) assuming a public/private hospital split of 47.1%/52.9%.	The effective EMP for lurbinectedin was reduced from $[redacted] per 2 mg vial to $[redacted] per 2 mg vial in the pre-PBAC response.

Data	Value	Source	Comments
Atezolizumab dispensed effective price per dose	Atezolizumab 3 weekly Public: $1,778.07 Private: $1,918.20 General: $1,849.77 S100 (CT): $1,686.84 Atezolizumab 4 weekly Public: $2,452.81 Private: $2,630.72	Based on an effective AEMP of $1,686.84 per vial (3 weekly) and $2,361.58 per vial (4 weekly) assuming a 75% rebate on the published AEMP per vial ($6,747.37; $9,446.30), and maximum amount dispensed.	Atezolizumab and durvalumab are subject to special pricing arrangements. The submission assumed a rebate of 75%.
Durvalumab dispensed effective cost per dose	Durvalumab 4 weekly Public: $2,781.81 Private: $2,978.14	Based on an effective AEMP of $2,361.58 per vial assuming a 75% rebate on the published AEMP ($3,587.44), and maximum amount dispensed.	
Average copayment	PBS: $14.63 RPBS: $7.61	Based on ES-SCLC maintenance therapy services for atezolizumab and durvalumab by beneficiary type in the 2024 calendar year.	-
PBS/RPBS distribution	PBS: 98.16% RPBS: 1.84%		-
Public/private hospital distribution	Public: 47.1% Private: 52.9%		The public/private hospital split used in the financial estimates was not consistent with the economic evaluation (48.1%/51.9%).
Medicine administration	$100.80	MBS item 13950 (administration of one or more antineoplastic agents). Fee: $126.00, 80% benefit $100.80.	-

Source: Section 4, pp187-200 of the submission; MS Excel 'Zepzelca_SCLC_BIM.xlsx', provided with the submission.
Abbreviations: ATE, atezolizumab; BSA, body surface area; CSR, clinical study report; CT, chemotherapy; DUR, durvalumab; EMP, ex-manufacturer price; ES-SCLC, extensive-stage small cell lung cancer; LUR, lurbinectedin; OS, overall survival; PBS, Pharmaceutical Benefits Scheme; PFS, progression free survival; RPBS, Repatriation Pharmaceutical Benefits Scheme; S100, Section 100; wkly, weekly.

6.62 Table 13 presents the estimated financial impact of listing lurbinectedin on the PBS. Revised estimates based on the updated effective EMP for the 2 mg vial presented in the pre-PBAC response are also provided.

Table 13: Estimated utilisation and financial impact of listing lurbinectedin

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated utilisation and financial impact of listing lurbinectedin						
Total lurbinectedin scripts[a]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost to the PBS/RPBS	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]
Estimated changes in financial impact of substituted atezolizumab and durvalumab						
Cost of atezolizumab as combination therapy with lurbinectedin	$[redacted][4]	$[redacted][4]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Cost offsets from atezolizumab/ durvalumab monotherapy	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net cost to the PBS/RPBS	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]
Overall net cost to the PBS/RPBS of listing lurbinectedin for ES-SCLC maintenance therapy						
Net cost of lurbinectedin	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost of atezolizumab and durvalumab	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted]	$[redacted][4]
Overall net cost to PBS/RPBS	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][5]
Net cost to MBS[d]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to PBS/RPBS/MBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][5]
Pre-PBAC response (2 mg vial = $485)						
Net cost to PBS/RPBS	$[redacted][4]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]

Source: Tables 116 to 119, pp191-193; Table 122, p195; Tables 123 to 125, pp196-197; Table 126, p197; and Table 132, p200 of the submission; MS Excel 'Zepzelca_SCLC_BIM.xlsx' provided with the submission.

Abbreviations: PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

[a] Based on projected utilisation of atezolizumab and durvalumab scripts, assuming uptake of 60% in Year 1, 70% in Year 2, 80% in Years 3-6, with script substitution for atezolizumab 3 weekly (11928T, 11929W, 14225Q, 14226R) as monotherapy to lurbinectedin 3 weekly (6.1 to 8.1 doses/course); atezolizumab (12076N, 12078Q) and durvalumab (13780G, 13766M) 4 weekly as monotherapy to lurbinectedin 3 weekly (4.58 to 8.1 doses/course).

[b] Based on a weighted average DPMA of $3,023.21.

[c] Based on an average PBS copayment of $4.63 (98.16% of scripts) and an average RPBS copayment of $7.61 (1.84% of scripts).

[d] MBS item 13950 (administration of one or more antineoplastic agents). Fee: $126.00, 80% benefit $100.80.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *5,000 to < 10,000*

[3] *$10 million to < $20 million*

[4] *$0 to < $10 million*

[5] *$20 million to < $30 million*

6.63 At year 6, the estimated net cost to the PBS was $20 million to < $30 million, with a total cost over 6 years of $100 million to < $200 million. Using the revised 2 mg vial price proposed in the pre-PBAC response, the total cost over 6 years was $70 million to < $80 million.

Quality Use of Medicine (QUM)

6.64 The DUSC noted that no quality use of medicine issues were presented by the submission. However, the DUSC noted the draft Product Information states the requirement for primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) to reduce the risk of febrile neutropenia (unless contraindicated) and advised prescriber education be provided regarding the routine use of G-CSF as prophylaxis for haematological toxicities.

Financial Management – Risk Sharing Arrangements

6.65 The submission stated that the sponsor is willing to enter into a risk sharing arrangement (RSA) for lurbinectedin in ES-SCLC. The submission noted that an RSA is currently in place for atezolizumab in ES-SCLC induction and maintenance therapy, with a cost-effectiveness-based expenditure cap (paragraphs 5.15 to 5.19 and 6.11, atezolizumab PSD, November 2019 PBAC meeting).

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

7 PBAC Outcome

7.1 The PBAC did not recommend lurbinectedin, in combination with atezolizumab, for first-line maintenance treatment of extensive-stage small cell lung cancer (ES-SCLC) in patients who have not progressed on or after first line induction therapy with atezolizumab, a platinum-based antineoplastic drug, and etoposide for listing on the PBS. The PBAC acknowledged the high clinical need for effective therapies for ES-SCLC; however, noted the small overall survival benefit and substantial toxicity demonstrated in the key trial compared to atezolizumab monotherapy. The PBAC considered that the economic model was overly optimistic, and highly sensitive to a number of inputs, which resulted in a high and uncertain incremental cost-effectiveness ratio (ICER). The PBAC considered that the utilisation estimates were reasonable.

7.2 The PBAC considered that the primary reason for this outcome was the economic evaluation. The PBAC considered that the base case ICER of $115,000 to < $135,000 per quality adjusted life year (QALY) presented in the submission was high and likely underestimated.

7.3 The PBAC acknowledged the consumer comments from health professionals, patient support organisations and professional organisations which were supportive of the submission and highlighted the high clinical need for effective treatments for this aggressive disease.

7.4 The PBAC considered that the nomination of atezolizumab as the comparator was appropriate but noted that durvalumab is also PBS listed for induction and maintenance therapy in this setting.

7.5 The PBAC noted that the submission was based on the results of the IMforte trial which was an open-label trial that compared lurbinectedin in combination with atezolizumab with atezolizumab monotherapy over a median follow up of 15 months.

7.6 The PBAC noted that lurbinectedin plus atezolizumab resulted in a statistically significant benefit over atezolizumab in both progression free survival (5.36 months versus 2.14 months; HR = 0.54; 95% CI: 0.43, 0.67) and overall survival (13.2 months vs 10.6 months; HR = 0.73; 85% CI: 0.57, 0.95). However, the PBAC considered that the magnitude of the benefit was small (3.22 month improvement in progression free survival and 2.6 month improvement for overall survival) and noted that the overall survival data were immature. The PBAC were also concerned that the benefit observed in the IMforte trial may not be realised in clinical practice as trial patients are generally fitter than those in the real world setting.

7.7 In terms of safety, the PBAC noted that lurbinectedin plus atezolizumab was associated with a higher incidence of any adverse event (97.1% vs 80.5%), Grade 3-4 adverse events (38.0% vs 22.0%%) and serious adverse events (31.0% vs 17%) than atezolizumab. Additionally, the PBAC noted that lurbinectedin plus atezolizumab was associated with a higher incidence of Grade 5 adverse events (i.e. death; 5% vs 2.5%).

7.8 The PBAC considered that although, on the basis of the IMforte trial, lurbinectedin plus atezolizumab was statistically significantly superior to atezolizumab in terms of effectiveness, the small clinical improvement in overall survival of 2.6 months was associated with a higher incidence of adverse events.

7.9 The PBAC considered that the base case ICER presented in the submission of $115,000 to < $135,000 per quality adjusted life year (QALY) was high. The PBAC noted that the economic model, although structurally sound, included a number of optimistic assumptions, including:

- a 7.5-year time horizon. The PBAC recalled that it had previously accepted a 5 year time horizon for atezolizumab (paragraph 7.12, atezolizumab PSD, July 2019 PBAC meeting). The PBAC noted that the pre-PBAC response included a 5 year time horizon;
- the use of Kaplan Meier data directly up to 14.95 months (the median duration of follow up). The PBAC noted that the model was sensitive to the point of extrapolation used; and
- that there was no convergence applied to the overall survival curves. The PBAC recalled that when considering atezolizumab, it had recommended curve convergence (paragraph 7.12, atezolizumab PSD, July 2019 PBAC meeting).

7.10 The PBAC noted that the revised base case presented in the pre-PBAC response, which included a 5-year time horizon and a reduced price of lurbinectedin, resulted in an ICER of $75,000 to < $95,000 per QALY. The PBAC considered that the ICER remained high and that lurbinectedin was not cost effective at the price proposed in the pre-PBAC response. The PBAC further noted that the ICER would increase when additional changes, such as amending the point of extrapolation and including curve convergence, were incorporated into the model.

7.11 The PBAC considered that the utilisation estimates for the use of lurbinectedin plus

atezolizumab as first-line maintenance therapy were reasonable.

7.12 The PBAC noted that the clinical landscape of ES-SCLC was changing and considered lurbinectedin, as monotherapy, may be better placed as a later line therapy after progression on or after prior platinum-containing therapy (as per current approved TGA indication).

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

Outcome:
Not recommended

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.