An addendum to this Public Summary Document has been included at the end of the document.

5.09 TARLATAMAB, Powder for injection 1 mg, Powder for injection 10 mg, Imdelltra®, Amgen Australia Pty Ltd

1 Purpose of submission

1.1 The Category 1 submission requested a Section 100 (Efficient Funding of Chemotherapy Program) Authority Required (STREAMLINED) listing of tarlatamab, for the treatment of patients with extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy (i.e. second-line or subsequent treatment).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus topotecan as a proxy for standard of care (SOC).

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

Component	Description
Population	ES-SCLC patients with disease progression on or after platinum-based chemotherapy (i.e. second-line or subsequent treatment).
Intervention	Tarlatamab 1 mg by intravenous infusion on Cycle 1 Day 1, followed by tarlatamab 10 mg by intravenous infusion on Cycle 1 Day 8 and Day 15, and then every 2 weeks until progression or unacceptable toxicity.
Comparator	Topotecan as a proxy for SOC chemotherapy.
Outcomes	Overall survival, progression-free survival, objective response rate, duration of response, patient-reported outcomes (disease-related symptoms of chest pain, cough and dyspnoea measured by the EORTC QLQ-LC13 and EORTC QLQ-C30; EQ-5D-5L and EQ-VAS) and safety.
Clinical claim	Tarlatamab is superior in terms of efficacy and safety compared with SOC chemotherapy.

Source: Table 1.1.1-1, p10 of the submission.
Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30; EORTC-QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13; ES-SCLC, extensive-stage small cell lung cancer; EQ-5D-5L, EuroQol 5-Dimension 5-Level questionnaire; SOC, standard of care; VAS, visual analogue scale.

2 Background

Registration status

2.1 Tarlatamab received provisional TGA approval on 26 June 2025 for the treatment of adult patients with ES-SCLC with disease progression on or after platinum-based chemotherapy. Provisional approval was based on the non-comparative, phase 2 DeLLphi-301 trial study (third-line treatment). Continued approval of this indication was dependent on verification and description of benefit in confirmatory trials.

2.2 The sponsor has since submitted the confirmatory DeLLphi-304 trial (second-line treatment) to the TGA to progress from provisional to full approval, with the Delegate's overview expected on 7 July 2026.

2.3 The proposed indication in the associated draft Product Information is for the treatment of adult patients with small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy, and does not limit treatment to extensive stage disease.

Previous PBAC consideration

2.4 Tarlatamab for third-line ES-SCLC (based on the DeLLphi-301 study) was submitted for consideration at the March 2025 PBAC meeting and was considered by the ESC and DUSC but withdrawn prior to consideration by the PBAC.

2.5 At the November 2025 meeting the PBAC did not recommend listing lurbinectedin (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[1].

3 Requested listing

3.1 The proposed listing with changes suggested by the Secretariat is shown below.

Initial treatment

MEDICINAL PRODUCT Form	PBS item code	Dispensed Price Max Amt	Max. Amount	№.of Rpts
TARLATAMAB Injection	NEW (Public) NEW (Private)	Public hospital $[redacted] Private hospital $[redacted]	1 mg	0
Available brands				
Imdelltra (Tarlatamab 1 mg injection, 1 vial)				
Imdelltra (Tarlatamab 10 mg injection, 1 vial)				
Category / Program: ☒ Section 100 – Efficient Funding of Chemotherapy – Public (IP)/ Private (IV)				
Prescriber type: ☒ Medical Practitioners				
Benefit type: ☒ Authority Required (Streamlined) *[new code]*				
Prescribing rule level:				
Administrative Advice: No increase in the maximum number of repeats may be authorised.				
Administrative Advice:				

[1] Pharmaceutical Benefits Scheme (PBS) | Recommendations made by the PBAC – November 2025

No increase in the maximum amount or number of units may be authorised.
Caution: Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).
Restriction Summary [new1] / Treatment of Concept: [new1A]
Indication: Extensive-stage small cell lung cancer
Treatment Phase: Initial treatment
Clinical criteria:
The condition must have progressed on or after treatment with a platinum-based chemotherapy (PBC)
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.
Prescribing Instructions: This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital setting
Prescribing Instructions: ~~Based on current PI:~~ According to the Therapeutic Goods Administration (TGA)-approved Product Information (PI), hospitalisation is recommended for at least 16 hours after (and during) the first infusion (on Day 1). Patients should remain within 1-hour of an appropriate healthcare setting and be accompanied by a caregiver for at least 24 hours after the first two doses (on Days 1 and 8). Subsequent doses may be monitored at the discretion of the treating clinician.
~~**Prescribing Instructions:**~~ ~~Alternative based on proposed PI:~~ ~~Monitor patients from the start of the infusion for 1 to 2 hours on Day 1 in an appropriate health care setting~~ ~~On Day 8 and subsequent infusions monitor patients at the discretion of the healthcare professional.~~ ~~Recommend that patients remain within 1-hour proximity of an appropriate healthcare setting for at least 24 hours from the start of infusion following Day 1 and Day 8 doses, accompanied by a caregiver.~~

Continuing and grandfather treatment

MEDICINAL PRODUCT Form	PBS item code	Dispensed Price Max Amt	Max. Amount	№.of Rpts
TARLATAMAB Injection	NEW (Public) NEW (Private)	Public hospital $[redacted] Private hospital $[redacted]	10 mg	6
Available brands				
Imdelltra (Tarlatamab 1 mg injection, 1 vial)				
Imdelltra (Tarlatamab 10 mg injection, 1 vial)				
Category / Program: ☒ Section 100 – Efficient Funding of Chemotherapy – Public (IP)/ Private (IV)				
Prescriber type: ☒ Medical Practitioners				
Benefit type: ☒ Authority Required (Streamlined) *[new code]*				
Prescribing rule level:				
Administrative Advice: No increase in the maximum number of repeats may be authorised.				
Administrative Advice: No increase in the maximum amount or number of units may be authorised.				
Caution:				

Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).
Restriction Summary [new2] / Treatment of Concept: [new2A]
Indication: Extensive-stage small cell lung cancer
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition,
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.
AND
Clinical criteria:
Patient must not have developed disease progression while being treated with this drug for this condition.
Prescribing Instructions: This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital setting
Restriction Summary [new3] / Treatment of Concept: [new3A]
Indication: Extensive-stage small cell lung cancer
Treatment Phase: ~~Transitioning from non-PBS to PBS-subsidised supply – Grandfather arrangements~~ *Transitioning from non-PBS to PBS-subsidised supply – Grandfather arrangements*
Clinical criteria:
Patient must have received non-PBS subsidised treatment with this drug for this PBS indication prior to [~~insert~~ listing date]
AND
Clinical criteria:
The condition must have progressed on or after treatment with a platinum-based chemotherapy (PBC)
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.
AND
Clinical criteria:
Patient must not have developed disease progression while being treated with this drug for this condition.
Prescribing Instructions: This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital setting

3.2 The submission proposed an effective ex-manufacturer price (EMP) of $[redacted] per 1 mg vial $[redacted] per 10 mg vial). The Pre-PBAC Response proposed a revised effective price and a special pricing arrangement for tarlatamab. The Pre-PBAC Response proposed a published EMP of $[redacted] per 1 mg vial ($[redacted] per 10 mg vial) and an effective EMP of $[redacted] per 1 mg vial ($[redacted] per 10 mg vial).

3.3 The requested restriction is narrower than the proposed TGA indication, which does not limit treatment to extensive stage disease. The key trial, DeLLphi-304, enrolled patients with Stage II SCLC (<0.5%) and Stage III SCLC (7.6%), with an unknown proportion of patients with Stage III SCLC meeting the criteria for ES-SCLC. The evaluation considered that there is a risk that tarlatamab may be used outside the proposed restriction in patients with limited stage SCLC.

3.4 The requested restriction includes a stopping rule excluding treatment with PBS subsidised tarlatamab after disease progression. This differed from the proposed TGA indication, which does not exclude treatment after further disease progression, and the DeLLphi-304 trial which allowed post-progression treatment with tarlatamab (approximately 40% of tarlatamab patients). The PBAC considered that the proposed stopping rule was reasonable.

3.5 Reflecting tarlatamab's positioning as a second or subsequent therapy for ES-SCLC, the proposed restrictions require that patients must have progressed on or after platinum-based chemotherapy (PBC). The restriction precludes access to patients with a clinical contraindication or intolerance to PBC. The PBAC considered that this was appropriate, noting that contraindications to PBC are rare.

3.6 In the requested initial treatment restriction, the submission proposed 2 alternative prescribing instructions for monitoring tarlatamab due to the risks of cytokine release syndrome (CRS) and neurological toxicity, based on the current and proposed TGA Product Information (PI) documents. The draft PI reduces the monitoring requirements following the first dose of tarlatamab from 16 to 1–2 hours, based on findings from a sub-study of the DeLLphi-304 trial. In the DeLLphi-304 trial, monitoring was required on Days 1 and 8 for 48 hours initially, which was subsequently reduced to 6 to 8 hours. The DeLLphi-304 clinical study report (CSR) noted that the reduced duration of monitoring did not alter the established CRS profile of tarlatamab including severity, time to intervention, time to resolution, and the outcome. The proposed change to the monitoring requirements in the PI have not yet been accepted by the TGA and the Delegate's overview was not available at the time of PBAC consideration (expected due date: 7 July 2026). The PBAC considered that the prescribing instruction outlining monitoring requirements should be consistent with the current TGA approved PI, i.e. 'Monitor patients from the start of the infusion for 16 hours on Cycle 1 Day 1 in an appropriate healthcare setting', and agreed with the submission that a hospital is the best placed setting in this circumstance.

3.7 The proposed clinical criteria limiting tarlatamab to second-line and subsequent therapy is consistent with the key DeLLphi-304 trial, which enrolled patients whose disease had progressed or recurred after a platinum-based regimen. However, the DeLLphi-304 trial enrolled patients with a baseline Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, and an estimated life expectancy of more than 12 weeks; requirements not included in the clinical criteria of the requested restriction. The evaluation considered that these differences, and the exclusion of limited-stage disease, may result in patients with a poorer prognosis being treated with tarlatamab on the PBS compared to patients in the DeLLphi-304 trial (see paragraph 6.46 for further detail on this topic). The ESC considered the generalisability of the trial to the proposed population was likely reasonable. However, the ESC considered that the inclusion of a criterion requiring patients to have a performance status of 0 or 1 in the proposed restriction may be appropriate.

3.8 The submission requested a maximum amount of 1 mg (i.e., 1 vial) with no repeats for the initial listing and a maximum amount of 10 mg (i.e., 1 vial) with 6 repeats for the continuing and grandfather listings. The submission noted that no repeats are proposed or needed for the initial therapy, since it accommodates for the 1 mg step dose administered on day 1. For the continuing treatment phase, the submission stated that 6 repeats would align with existing listings for PD-L1 inhibitor drugs that provide sufficient repeats for either 3 x 3 weekly cycles (i.e. 9 weeks of therapy) or 3 x 4 weekly cycles (i.e. 12 weeks of therapy). The ESC noted that 6 repeats would allow for 7 x 2 weekly cycles (i.e. 14 weeks of therapy) and considered that the number of repeats could be reduced, given the median time to a response for tarlatamab is 6 weeks, based on both the DeLLphi-301 and DeLLphi-304 clinical trials (paragraphs 6.29 and 6.24, respectively).

3.9 The submission requested a grandfather provision to allow eligible patients who may have initiated tarlatamab prior to its PBS listing (e.g. accessing through private prescription or a sponsor-supported program) to receive PBS treatment with tarlatamab. The submission did not provide an estimate of the potential number of patients requiring grandfathered treatment. The PBAC considered that the grandfather listing should allow patients who had previously received treatment via compassionate access means, to be able to bypass the monitoring requirements required during the first treatment cycle.

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

4 Population and disease

4.1 The Australian Institute of Health and Welfare (AIHW) estimated there would be 15,108 new cases of lung cancer diagnosed in 2025, representing 9% of all cancer diagnoses in Australia (AIHW, 2023). Lung cancer is differentiated on biopsy or cytology into two broad categories: non-small cell lung cancer (NSCLC), and SCLC. The submission noted that SCLC represents approximately 11.75% of all lung cancer cases (AIHW 2011).

4.2 SCLC is a poorly differentiated, neuroendocrine carcinoma, characterised by rapid disease progression, rapid tumour growth, and early development of metastases to multiple organ systems and lymph nodes (commonly involving the brain, liver or bone). SCLC is categorised into two broad prognostic groups:

- Limited stage disease (LS-SCLC), confined to an ipsilateral hemithorax with or without spread to mediastinal lymph nodes (broadly captured in SCLC tumour, nodes and metastasis [TNM] Stages 1–3).
- Extensive stage disease (ES-SCLC), includes all SCLC not confined to the origin ipsilateral hemithorax, including malignant pleural/pericardial effusion or hematogenous metastases and/or metastases in extrathoracic organs or

tissues (NCCN 2024; broadly captured in SCLC TNM Stage 4, including all SCLC with related extrathoracic metastasis).

4.3 Approximately 71.3% of patients with SCLC present with ES-SCLC at diagnosis. Of the remaining 28.7% of patients with limited stage disease, an estimated 75% will progress to ES-SCLC (Rudin et al. 2021; Wang et al. 2023; Blackall et al. 2023). Prognosis in SCLC is poor and dependent on disease progression at diagnosis. UpToDate (2025) reports that median survival for patients with LS-SCLC ranges from 15 to 30 months, with 5 year survival of 10% to 13%; and median survival for patients with ES-SCLC ranges from 8 to 13 months, with 5 year survival of 1% to 2%.

4.4 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). The median age at diagnosis for patients presenting with ES-SCLC has increased over the last decade from 65 years to 69 years (Wang et al. 2023; Blackall et al. 2023). While most cases of ES-SCLC are initially sensitive to chemotherapy, relapse is frequent, and the overall mortality rate is high (National Cancer Institute 2023).

4.5 The clinical management algorithm positions tarlatamab as an alternative second-line or subsequent therapy for patients with ES-SCLC, following first-line treatment with a platinum-based chemotherapy plus etoposide (with or without an immune checkpoint inhibitor) for platinum resistant/refractory or platinum sensitive patients. Treatment with tarlatamab would be in place of rechallenge with a platinum-based chemotherapy plus etoposide or another non-platinum chemotherapy (typically topotecan, cyclophosphamide plus doxorubicin plus vincristine [CAV], or irinotecan).

4.6 The submission stated that it is anticipated that most use of tarlatamab will be as a second-line therapy, with a minority of patients receiving tarlatamab in subsequent lines of therapy.

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

5 Comparator

5.1 The submission nominated SOC as the main comparator. In Australian clinical practice, SOC chemotherapies include a platinum-based therapy (cisplatin/carboplatin) plus etoposide, CAV, and irinotecan or topotecan, with no single therapy predominating. In the DeLLphi-304 trial, SOC chemotherapies included topotecan (used in 72% of patients), lurbinectedin (18%), and amrubicin (9%). Topotecan was proposed as a proxy for SOC chemotherapies (largely for the purpose of the economic evaluation) given it is available and widely used in Australia, was the predominant comparator therapy administered in the key DeLLphi-304 trial, and lurbinectedin and amrubicin are not widely used in Australia. The submission claimed that other chemotherapies

used for second-line and subsequent treatment in Australia (including platinum plus etoposide, CAV, and irinotecan) are similar in efficacy to topotecan. The ESC considered that SOC, as defined in the submission, was an appropriate choice of comparator.

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. Two thoracic medical oncologists described the severity of the condition, poor prognosis and impact on patients' quality of life under the current standard of care. The clinicians emphasised the significant unmet need of the patient population and persisting lack of treatment advances in ES-SCLC. The hearing highlighted concerns with current second line treatments in SCLC which have limited benefit, significant side effects and toxicity. The clinicians described their experiences of patients involved in tarlatamab clinical trials and the observed benefits including symptom relief, improved quality of life and durability of treatment. While the potential side effects and initial toxicity of tarlatamab was acknowledged, the clinicians considered them to be of a short duration and preferrable to alternative second line chemotherapies which result in continuous toxicity and enduring side effects. The hearing highlighted the patient group as hopeful and motivated to engage in an effective second line treatment, the clinicians viewed tarlatamab as potentially transformative for people with ES-SCLC.

Consumer inputs

6.2 The PBAC noted and welcomed input from health care professionals (9), individuals who would like access to tarlatamab (2) and medical (1) and consumer (2) organisations via the Office of Health Technology Assessment Consultation Hub.

6.3 Health care professionals highlighted the high clinical need for patients with ES-SCLC, noting that patients currently have limited treatment options with only modest benefit and typically experience rapidly progressive disease, profound symptom burden and extremely limited survival. Health care professionals noted the improved clinical responses and overall survival observed in tarlatamab clinical trial patients compared with SOC and considered that these improvements were clinically meaningful and vitally important for patients and their families. Health care professionals considered the toxicity profile to be predictable, monitorable, and manageable in real-world oncology settings. Comments noted that the availability of tarlatamab on the PBS would help to reduce geographical inequities in cancer outcomes for patients currently living in rural and remote communities, noting that many patients must travel long distances to access clinical trials. Comments noted that the availability of tarlatamab on the PBS would allow patients to remain closer to

home and be supported by family and carers. This would lessen the emotional, financial, and logistical burden of treatment, benefiting both patients and their families and caregivers. One health care professional noted that in their state, regional oncology services had recently developed additional capabilities and would be prepared to monitor and manage CRS and immune effector cell-associated neurotoxicity syndrome (ICANS). However, other comments noted that some smaller rural centres may not have the resources to develop the additional infrastructure required to monitor and treat CRS and ICANS.

6.4 Individuals who would like access to tarlatamab described the physical and emotional burden associated with SCLC. Comments described the side effects associated with current therapies (chemotherapy and radiotherapy) and noted that these have made it difficult for them to maintain their normal routines and connect with friends and family. Individuals considered that tarlatamab would extend their lifespan.

6.5 The Thoracic Group of Australasia (TOGA), Lung Foundation Australia and Lung Cancer Australia expressed support for the proposed PBS listing of tarlatamab. Comments highlighted the high clinical need for patients with ES-SCLC, noting that patients experience a high physical and emotional burden, with current SOC providing only modest clinical benefit and poor survival outcomes and are often poorly tolerated. Comments noted the clinical benefits associated with tarlatamab vs SOC observed in the DELLphi-304 clinical trial. Comments also considered that tarlatamab had a distinct safety profile that may present acute toxicity management, cost and implementation challenges in routine Australian practice. Comments noted that due to the safety profile of tarlatamab and this being a new class of drug for the lung cancer sector, there will be the need for workplace education on identifying and managing the safety profile. However, the comments stated that overall tarlatamab remained better tolerated with side effects commonly only occurring early in the treatment process making them more predictable compared to current treatment options which are cumulative and ongoing.

Clinical trials

6.6 The submission was based on a head-to-head phase 3, open-label, randomised trial comparing tarlatamab to SOC chemotherapy in SCLC patients with disease progression or recurrence following a platinum-based regimen (DeLLphi-304).

6.7 The submission also presented supportive evidence from the phase 2, single arm tarlatamab study in third-line ES-SCLC patients (DeLLphi-301), including the results of indirect analyses comparing tarlatamab from the DeLLphi-301 study with SOC chemotherapy from 2 retrospective registry studies (Cancer Analysis System [CAS] cohort 2023; Flatiron study 2024). This evidence was provided as supportive evidence of the efficacy of tarlatamab in third-line and subsequent therapy.

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
DeLLphi-304 (NCT05740566)	A randomized, open-label, phase 3 study of tarlatamab compared with standard of care in subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy (DeLLphi-304). Mountzios G, Sun L, Cho BC, et al. Tarlatamab in small-cell lung cancer after platinum-based chemotherapy.	Clinical study report, May 2025. Clinical study report addendum, June 2025. *New England Journal of Medicine* 2025; 393:349-361.
Supportive evidence		
DeLLphi-301 (NCT05060016)	A phase 2 study evaluating the efficacy, safety, tolerability, and pharmacokinetics of tarlatamab in subjects with relapsed/refractory small cell lung cancer after two or more prior lines of treatment (DeLLphi-301). Ahn MJ, Cho BC, Felip E, et al. Tarlatamab for patients with previously treated small-cell lung cancer.	Clinical Study Report, September 2023. Clinical study report addendum, March 2024. *New England Journal of Medicine* 2023; 389(22): 2063-2075.
CAS study 2023	A retrospective cohort study assessing patient demographics, clinical characteristics, treatment patterns, outcomes, adverse events, and all-cause healthcare resource utilisation (HCRU) in patients with small-cell lung cancer in England using the Cancer Analysis System.	Sponsor data on file (20220199), March 2023.
Flatiron study 2024	Tarlatamab vs. real-world physicians' choice of therapies in patients with relapsed or refractory small cell lung cancer after two or more prior lines of treatment: patient-level indirect treatment comparison (ITC) of DeLLphi-301 vs. Flatiron real-world data.	Sponsor data on file (20240049), March 2024.

Source: Table 2.2.2-1, p29 of the submission. Attachment 2.2 of section 2 in the submission
Note: Citations relating to conference abstracts omitted.

6.9 The key features of the DeLLphi-304 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 modelled evaluation
DeLLphi-304	509	Phase 3, multicentre, open label, randomised controlled trial. Median follow-up of up to 14 months.	High	Adult patients with recurrent SCLC following one platinum-based regimen.	Overall survival, progression-free survival, objective response rate, duration of response, patient-reported outcomes, adverse events	PFS, OS, TTD, adverse events, EQ-5D-5L

Source: Section 2.3, pp31-35 of the submission.
Abbreviations: OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer; TTD, time to treatment discontinuation.

6.10 The DeLLphi-304 trial is an ongoing international, open-label, randomised, controlled trial comparing tarlatamab with standard of care chemotherapy in patients with relapsed SCLC after first-line treatment with a platinum-based chemotherapy. The expected study completion date is March 2028.

6.11 The DeLLphi-304 trial had a high risk of bias. The open-label trial design has the potential to introduce bias, as knowledge of treatment assignment may affect disease management decisions and investigator-assessed outcomes.

6.12 In the DeLLphi-304 trial, tarlatamab was administered as a 60-minute intravenous infusion initiated with a step-up dose of 1 mg on day 1 of cycle 1, followed by 10 mg

on days 8 and 15 of cycle 1 and then 10 mg every 2 weeks thereafter, consistent with the current tarlatamab Product Information. For the first two infusions, patients were initially monitored in the hospital for 48 hours, which was subsequently reduced through a protocol amendment to 6 to 8 hours of surveillance in the outpatient setting. Less intensive monitoring is recommended in the current tarlatamab Product Information (16 hours after the first infusion, with patients remaining within 1 hour of an appropriate healthcare setting for 24 hours after each infusion on Day 1 and Day 8, accompanied by a caregiver), and the draft tarlatamab Product Information (1–2 hours after infusions on Day 1 in an appropriate healthcare setting, and at the discretion of the health care provider on Day 8 and subsequent infusions).

6.13 The dosing and administration of tarlatamab in DeLLphi-304 was subject to protocol driven dose reduction, interruption or permanent discontinuation, based on the symptoms of CRS, and ICANS, or other treatment related serious adverse events, and response to prespecified management protocols.

6.14 The DeLLphi-304 trial was limited to patients with an ECOG performance status of 0 or 1, and patients were required to have a minimum life expectancy of 12 weeks. The trial also included a small proportion of patients with limited-stage disease (9%). The proposed PBS restriction does not include criteria for ECOG performance status or minimum life expectancy and the use of tarlatamab is restricted to patients with extensive-stage disease. These differences may result in patients with a poorer prognosis being treated with tarlatamab on the PBS compared to patients in the DeLLphi-304 trial, with an uncertain impact on the magnitude of benefit.

6.15 In the DeLLphi-304 trial, treatment beyond radiological progression was permitted if the investigator judged it would be of benefit to the patient, and 40% of patients with disease progression in the tarlatamab arm continued treatment with tarlatamab beyond progression. This is inconsistent with the current and draft tarlatamab Product Information documents and proposed restriction, which does not allow treatment post-progression. Patients treated with tarlatamab after progression received more cycles of therapy and a longer duration of active treatment (post-progression tarlatamab (n=77) - median 8.0 cycles over 28.14 weeks; safety analysis set (n=252) - median 5.0 cycles over 18.2 weeks). Treatment with tarlatamab was associated with relatively small improvements in progression-free survival (PFS; median difference 1.0 months; see Table 5 below) compared to improvements in overall survival (OS; median difference 5.2 months; see Table 4 below). The evaluation considered that the extent to which post-progression treatment affected tarlatamab OS benefits was unclear. The evaluation also considered that the additional analysis conducted for the economic model, censoring tarlatamab OS data at post-progression tarlatamab use, was poorly documented. The Pre-Sub-Committee Response (PSCR) maintained that post-progression treatment with tarlatamab had minimal impact on OS and provided a comparison of patient characteristics for those who continued versus discontinued tarlatamab treatment upon disease progression, as well as additional analyses of OS, PFS, and time to treatment discontinuation (TTD) by post-progression treatment status.

6.16 The additional data provided in the PSCR indicated that there were differences in baseline characteristics for patients who received tarlatamab treatment post-progression compared to those who discontinued treatment; patients were younger (18–74 years 92.8% vs 83.4%), with a higher percentage female (29.8% vs 25.2%), a longer duration of response to prior platinum-based therapy (≥180 days 88.1% vs 63.5%), a smaller percentage with liver metastases (22.6% vs 47.0%), and larger percentages with brain metastases (56.0% vs 35.7%), current smokers (25% vs 15.7%), and prior radiological treatment (67.9% vs 54.8%). There were also differences in outcomes in the DeLLphi-304 trial, where patients treated post-progression vs those that discontinued had a longer duration progression-free (mean 5.0 vs 2.8 months) and of overall survival (mean 13.9 vs 8.3 months) for patients who received post-progression tarlatamab compared to those who discontinued at disease progression (see paragraph 6.56 for detail related to the economic model).

Comparative effectiveness

6.17 Results for the DeLLphi-304 trial were presented for the primary analysis (data cutoff date: 29 January 2025) and updated analyses at the subsequent follow-up, where available (data cutoff date: 29 April 2025).

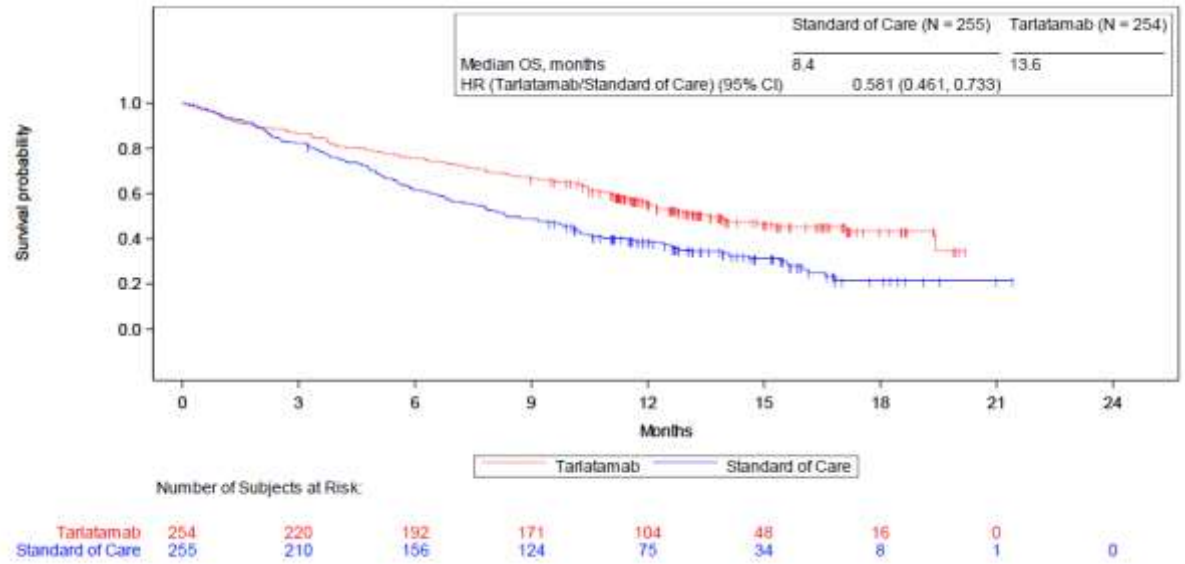
6.18 Table 4 and Figure 1 below present the results of overall survival in the DeLLphi-304 trial.

Table 4: Overall survival in the DeLLphi-304 trial (ITT; 29 January 2025 and 29 April 2025 data cuts)

	Tarlatamab (N=254)	SOC (N=255)
Overall survival (data cut-off 29 January 2025)		
Median duration of follow-up, months (95% CI)	11.2 (10.4, 12.1)	11.7 (10.6, 12.3)
Participants with event, n (%) - Death - Censored	 111 (43.7) 143 (56.3)	 152 (59.6) 103 (40.4)
Median overall survival, months (95% CI)	13.6 (11.1, NE)	8.3 (7.0, 10.2)
Hazard ratio (95% CI) [a]	**0.599 (0.468, 0.768)**	
Overall survival (data cut-off 29 April 2025)		
Median duration of follow-up, months (95% CI)	13.8 (13.2, 14.7)	14.3 (13.2, 15.2)
Participants with event, n (%) - Death - Censored	 127 (50.0) 127 (50.0)	 173 (67.8) 82 (32.2)
Median overall survival, months (95% CI)	13.6 (11.9, NE)	8.4 (7.2, 10.2)
Hazard ratio (95% CI) [a]	**0.581 (0.461, 0.733)**	
Kaplan-Meier overall survival estimate, % (95% CI) - At 6 months - At 12 months - At 18 months	 75.6 (69.8, 80.4) 55.8 (49.4, 61.8) 43.3 (35.4, 50.9)	 61.5 (55.2, 67.1) 38.9 (32.8, 44.9) 21.5 (14.4, 29.5)

Source: Table 2.5.1-1, p46 of the submission; Table 14-4.1.1, pp7-8 of DeLLphi-304 CSR Additional tables (April 2025 data cut).
Abbreviations: CI, confidence interval; ITT, intention to treat; NE, not estimable; SOC, standard of care.
Bolded results were statistically significant.
[a] Hazard ratio and 95% CIs estimated using a stratified Cox proportional hazards model.

Figure 1: Overall survival in the DeLLphi-304 trial (ITT; 29 April 2025 data cut)



Source: Figure 2.5.1-2, p47 of the submission.
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; OS, overall survival.

6.19 At the January 2025 data cut, based on a median follow up of 11.2 months in the tarlatamab arm and 11.7 months in the SOC chemotherapy arm, treatment with tarlatamab was associated with a statistically significant improvement in overall survival compared to SOC (hazard ratio [HR]: 0.599; 95% confidence interval [CI]: 0.468, 0.768). Median overall survival was 13.6 months in the tarlatamab arm, compared to 8.3 months in the SOC arm.

6.20 Results based on the April 2025 data cut (HR: 0.581; 95% CI: 0.461, 0.733) and the post hoc comparison of tarlatamab and the topotecan SOC subgroup, used in the economic evaluation (HR: 0.540; 95% CI: 0.421, 0.691; April 2025 data cut), were slightly more favourable than the earlier data cut.

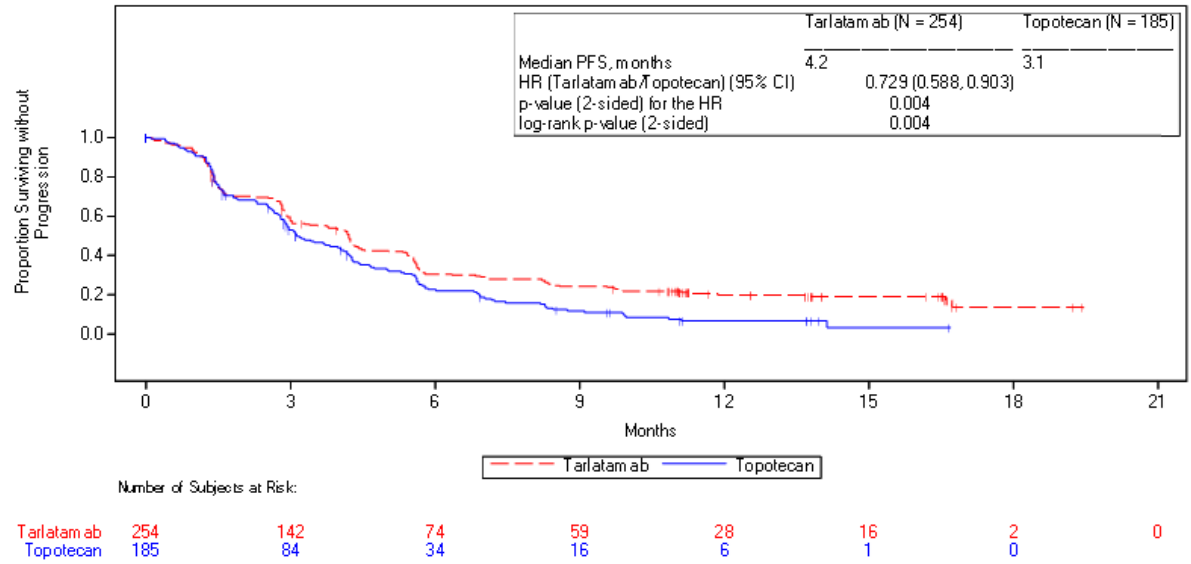
6.21 Table 5 and Figure 2 below present the results for the key secondary outcome of PFS in the DeLLphi-304 trial.

Table 5: Investigator assessed progression-free survival in the DeLLphi-304 trial (ITT; 29 January 2025 and 29 April 2025 data cuts)

	Tarlatamab (N=254)	SOC (N=255)
Progression-free survival (data cut-off 29 January 2025)		
Median duration of follow-up, months (95% CI)	11.0 (8.5, 11.2)	9.7 (8.4, 11.1)
Participants with events, n (%) - Death - Disease progression - Censored	191 (75.2) 25 (9.8) 166 (65.4) 63 (24.8)	205 (80.4) 41 (16.1) 164 (64.3) 50 (19.6)
Median progression-free survival, months (95% CI)	4.2 (3.0, 4.4)	3.2 (2.9, 4.2)
Hazard ratio (95% CI)[a]	**0.716 (0.586, 0.875)**	
Progression-free survival (data cut-off 29 April 2025)		
Median duration of follow-up, months (95% CI)	13.7 (11.3, 14.1)	13.7 (11.1, 14.0)
Participants with events, n (%) - Death - Disease progression - Censored	199 (78.3) 26 (10.2) 173 (68.1) 55 (21.7)	212 (83.1) 41 (16.1) 171 (67.1) 43 (16.9)
Median progression-free survival, months (95% CI)	4.2 (3.0, 4.4)	3.2 (2.9, 4.2)
Hazard ratio (95% CI)[a]	**0.699 (0.574, 0.852)**	
Kaplan-Meier PFS estimate, % (95% CI) - At 6 months - At 12 months - At 18 months	 30.4 (24.8, 36.2) 24.3 (19.1, 29.8) 19.9 (15.0, 25.2)	 22.8 (17.5, 28.5) 10.2 (6.6, 14.8) 4.9 (2.4, 8.8)

Source: Table 2.5.1-2, p50 of the submission; Table 14-4.1.1, p10 of DeLLphi-304 CSR Additional tables (April 2025 data cut).
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; PFS, progression-free survival; SOC, standard of care.
Bolded results were statistically significant.

Figure 2: Investigator assessed progression-free survival in the DeLLphi-304 trial (ITT; 29 April 2025 data cut)



Source: Figure 2.5.1-6, p51 of the submission.
Abbreviations: CI, confidence interval HR, Hazard ratio; ITT, intention to treat; PFS, progression-free survival.

6.22 At the January 2025 data cut, based on a median follow up of 11.0 months in the tarlatamab arm and 9.7 months in the SOC chemotherapy arm, treatment with tarlatamab was associated with a statistically significant improvement in PFS compared with SOC chemotherapy (HR: 0.72; 95% CI: 0.59, 0.88). Median PFS was 4.2 months in the tarlatamab arm and 3.2 months in the SOC arm.

6.23 Results based on the April 2025 data cut (HR: 0.699; 95% CI: 0.574, 0.852) were slightly more favourable, and the post hoc comparison of tarlatamab and the topotecan SOC, used in the economic evaluation (HR: 0.729; 95% CI: 0.588, 0.903; April 2025 data cut), slightly less favourable, than the earlier data cut.

6.24 The ESC noted that median time to objective response was 1.5 months in the tarlatamab arm and 1.4 months in the SOC arm (the same for both data cut-off dates). The ESC also noted that the median duration of response for the tarlatamab arm was 6.9 months in the tarlatamab arm and 5.5 months in the SOC arm (based on the 29 January 2025 data cut-off; at the 29 April 2025 data cut-off, median duration of response was 7.1 months for tarlatamab and unchanged for SOC).

6.25 Key patient reported outcomes were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire Lung Cancer module (EORTC QLQ-LC13) and Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). The Dyspnoea composite score combines 4 questions from EORTC QLQ-LC13 and EORTC QLQ-C30 regarding shortness of breath. Scores range between 0–100, with a higher score representing a greater symptom burden. After 18 weeks from baseline, treatment with tarlatamab was associated with a small numerical improvement in dyspnoea scores, while the SOC arm demonstrated a worsening in dyspnoea scores over time, with a statistically significant difference between treatment arms (least squares mean change: -9.14; 95% CI -12.64, -5.64).

6.26 For EORTC QLQ-LC13 Cough, 16.1% of patients in the tarlatamab arm had improved responses after 18 weeks from baseline, compared to 9.0% of SOC patients, a statistically significant difference (odds ratio 2.04; 95% CI 1.17, 3.55). For EORTC QLQ-LC13 Chest pain, 8.7% of patients in the tarlatamab arm had improved responses after 18 weeks from baseline, compared to 3.5% of SOC patients, however, the difference did not reach statistical significance (odds ratio 1.84; 95% CI 0.89, 3.81).

6.27 Due to the hierarchical testing strategy, subsequent outcomes were not formally tested, and the results were considered descriptive. After 18 weeks from baseline , tarlatamab was associated with numerically smaller deterioration in EORTC QLQ-C30 Physical Functioning and Global Health Status/Quality of Life subscales compared to SOC. EQ-5D VAS scores were comparable at baseline between the tarlatamab and SOC treatment arms. After 18 weeks from baseline, tarlatamab was associated with a numerically smaller deterioration in EQ VAS from baseline compared to SOC. The submission did not provide EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L) index scores by treatment arm.

6.28 The ESC noted that the submission presented the results of the DeLLphi-301 study (02 October 2023 data cut previously considered by the ESC at the March 2025 meeting), as supportive evidence of the efficacy of tarlatamab in third-line and subsequent therapy. The submission referred to an October 2024 data cut for the DeLLphi-301 study, but these data were not provided with the submission.

6.29 The ESC noted that the objective response rate for tarlatamab (10 mg) was 40.4% (based on the 27 June 2023 data cut-off; 41.4% at the 2 October 2023 data cut-off)

and the median time to response was 1.4 months (2 October 2023 cut-off). The ESC also noted the proportions of patients having a duration of response was at least 6 and 9 months (based on tarlatamab 10 mg and 100 mg arms combined, based on the 27 June 2023 data cut-off).

6.30 Based on the October 2023 data cut, the median overall survival for tarlatamab (10 mg cohort) was 15.2 months (median follow-up of 13.8 months), and median PFS was 4.3 months (median follow-up of 13.6 months).

6.31 The results of an unanchored matching adjusted indirect comparison (MAIC) comparing efficacy outcomes for tarlatamab 10 mg from the DeLLphi-301 study with SOC based on data from the CAS 2023 registry study and a supportive propensity score adjusted indirect comparison comparing efficacy outcomes for tarlatamab 10 mg from the DeLLphi-301 10 mg cohort with SOC based on data from the Flatiron (2024) registry study are presented in Table 6.

Table 6: Key primary and secondary outcomes of the DeLLphi-301 (CAS and Flatiron cohorts)

Outcomes	Tarlatamab vs SOC	
	CAS 3L cohort (MAIC) [b] HR (95% CI)	Flatiron cohort (weighted)[c] HR (95% CI)
Overall survival	0.305 (0.166, 0.561)	0.45 (0.30, 0.68)
Progression-free survival[a]	0.184 (0.100, 0.338)	0.61 (0.43, 0.90)

Source: Table 2.7.1-2, p69 of the submission.

Abbreviations: CAS, Cancer Analysis System; CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; SOC, standard of care.

[a] Time-to treatment discontinuation or death was used as a proxy for progression-free survival in the CAS cohort.

[b] DeLLphi 301 data cutoff Oct 2023. MAIC analysis adjusted for age at index, sex, ECOG performance status at index, brain metastases (at index for tarlatamab; at 1L for CAS cohort SOC), liver metastases (at index for tarlatamab; at 1L for CAS cohort SOC), disease stage at diagnosis, time from diagnosis to index.

[c] DeLLphi 301 data cutoff Oct 2023. After weighting imbalances between cohorts for potential confounding variables adjusted for age at index, sex, smoking history prior to index, ECOG PS at index, number of previous lines of therapy, CFI after 1L therapy, time from SCLC diagnosis to index, TNM stage at diagnosis, and brain metastasis.

6.32 The ESC recalled it had previously considered that the results of the unanchored MAICs of tarlatamab versus SOC were supportive of a claim of superior effectiveness, however the magnitude of benefit was unclear due to the substantial uncertainty related to the following: low effective sample size (ESS = 27.05 patients; suggesting a lack of overlap between DeLLphi-301 and the CAS SOC cohort study), the potential for bias due to failure to match all relevant prognostic and treatment-effect modifier variables (such as number of prior lines of therapy, baseline life expectancy of at least 12 weeks, and smoking status), the use of time to treatment discontinuation as a proxy for PFS in the CAS cohort, and the uncertain impact of continued use of tarlatamab post-progression in 50% of progressed patients in DeLLphi-301. The ESC also recalled it previously considered that the applicability of the matched population to the proposed PBS population was similarly uncertain (Main issues for PBAC consideration, tarlatamab ESC Advice, March 2025 PBAC meeting).

6.33 The submission claimed that the efficacy of tarlatamab observed in patients treated with third-line tarlatamab in the DeLLphi-301 study was consistent with the results of the DeLLphi-304 trial. However, comparison of the tarlatamab survival curves from the DeLLphi-301 study and DeLLphi-304 trial, conducted in different lines of therapy

may not be informative, due to inherent survivorship bias associated with patients who were fit enough to initiate a third-line therapy in the DeLLphi-301 study.

Comparative harms

6.34 Table 7 presents the key adverse events reported in the DeLLphi-304 trial based on the January 2025 and April 2025 data cuts.

Table 7: Summary of key adverse events in DeLLphi-304 (safety analysis set; 29 January 2025 and 29 April 2025 data cuts)

TEAEs, n (%)	January 2025 data cut		April 2025 data cut	
	Tarlatamab (N=252)	SOC (N=244)	Tarlatamab (N=252)	SOC (N=244)
All TEAEs	249 (98.8)	243 (99.6)	249 (98.8)	243 (99.6)
Grade ≥3 adverse events	136 (54.0)	195 (79.9)	141 (56.0)	195 (79.9)
Serious adverse events	129 (51.2)	125 (51.2)	131 (52.0)	126 (51.6)
TEAEs leading to dose interruption and/or reduction	94 (37.3)	159 (65.2)	96 (38.1)	159 (65.2)
TEAEs leading to discontinuation	13 (5.2)	30 (12.3)	14 (5.6)	31 (12.7)
Fatal adverse events	20 (7.9)	21 (8.6)	20 (7.9)	21 (8.6)
Treatment-related TEAEs	235 (93.3)	223 (91.4)	235 (93.3)	223 (91.4)
- Grade ≥3 adverse events	67 (26.6)	152 (62.3)	68 (27.0)	152 (62.3)
- Serious adverse events	70 (27.8)	75 (30.7)	71 (28.2)	76 (31.1)
- AEs leading to dose interruption and/or reduction	48 (19.0)	134 (54.9)	48 (19.0)	134 (54.9)
- AEs leading to discontinuation	7 (2.8)	15 (6.1)	8 (3.2)	16 (6.6)
- Fatal adverse events	1 (0.4)	4 (1.6)	1 (0.4)	4 (1.6)
TEAEs of interest				
Cytokine release syndrome (broad)[a]	235 (93.3)	208 (85.2)	235 (93.3)	208 (85.2)
Cytokine release syndrome (narrow)[b]	142 (56.3)	3 (1.2)	142 (56.3)	3 (1.2)
Grade ≥4	0	0	0	0
Grade ≥3	3 (1.2)	0	3 (1.2)	0
Grade ≥2	35 (13.9)	1 (0.4)	35 (13.9)	1 (0.4)
Serious adverse events	42 (16.7)	1 (0.4)	43 (17.1)	0
Leading to dose interruption	4 (1.6)	1 (0.4)	4 (1.6)	0
Leading to discontinuation	1 (0.4)	0	1 (0.4)	0
Serious	1 (0.4)	0	1 (0.4)	0
Hypersensitivity[b]	36 (14.3)	28 (11.5)	36 (14.3)	29 (11.9)
ICANS[b]	15 (6.0)	2 (0.8)	15 (6.0)	2 (0.8)
Neurological events[b]	140 (55.6)	86 (35.2)	142 (56.3)	86 (35.2)
Neutropenia[b]	52 (20.6)	124 (50.8)	52 (20.6)	124 (50.8)

Source: Table 2.5.2.2, pp58-59 of the submission; Table 12-6, pp132-137 of DeLLphi-304 CSR (January 2025 data cut); Table 14-6.1.1, p17 and Table 14-6.6.2, pp134-150 of DeLLphi-304 CSR Additional tables (April 2025 data cut).

Abbreviations: AE, adverse event; ICANS, immune effector cell associated-neurotoxicity syndrome; MedDRA, Medical Dictionary for Regulatory Activities; SOC, standard of care; TEAE, treatment emergent adverse event.

[a] Events identified by broad search for preferred terms in the MedDRA.

[b] Events identified by narrow search for preferred terms in the MedDRA.

6.35 In the DeLLphi-304 trial (January 2025 data cut), almost all patients experienced an adverse event (98.8% in the tarlatamab arm; 99.6% in the SOC arm). Treatment-emergent adverse events reported in at least 10% more patients in the tarlatamab arm compared to the SOC arm were cytokine release syndrome, decreased appetite, pyrexia and dysgeusia (distortion in taste). Anaemia, neutropenia and leukopenia

were adverse events reported in at least 10% more patients in the SOC arm compared to the tarlatamab arm.

6.36 The majority of patients in the DeLLphi-304 trial experienced serious adverse events (51.2% in each arm). Serious adverse events reported in at least 5% of patients in either arm were febrile neutropenia (tarlatamab 2.0%; SOC 9.8%), pyrexia (tarlatamab 5.6%; SOC 0%), CRS (tarlatamab 17.1%; SOC 0.4%), and pneumonia (tarlatamab 4.0%; SOC 8.6%).

6.37 Fatal adverse events were reported in 20 (7.9%) patients in the tarlatamab arm and 21 (8.6%) patients in the SOC arm. Treatment-related fatal adverse events were reported in 1 patient in the tarlatamab arm (0.4%; ICANS) and 4 patients in the SOC arm (1.6%; general physical health deterioration, pneumonia, respiratory tract infection, and tumour lysis syndrome).

6.38 For adverse events of interest, higher proportions of patients in the tarlatamab arm compared to the SOC arm of the DeLLphi-304 trial experienced CRS (narrow: 56.3% versus 1.2%; broad: 93.3% versus 85.2%) and neurological events (55.6% versus 35.2%), including ICANS (6.0% versus 0.8%). The incidence of neutropenia was lower in the tarlatamab arm compared to the SOC arm (20.6% versus 50.8%).

6.39 The incidence of adverse events at the April 2025 data cut was consistent with the earlier data cut.

6.40 The submission noted that during the DeLLphi-304 trial, a protocol amendment allowed the reduction of inpatient monitoring from 48 hours to 6–8 hours for the first 2 administrations of tarlatamab (Day 1 and Day 8). Overall, 43 (16.9%) tarlatamab patients were enrolled under the 6–8 hour monitoring criteria. The evaluation noted that the reduction in the duration of inpatient monitoring during cycle 1 did not appear to worsen the CRS safety profile of tarlatamab. The submission noted that further reductions in inpatient monitoring will be proposed as information becomes available throughout the tarlatamab clinical trial program, including the proposed 1–2 hour monitoring period in the most recent TGA application.

6.41 The ESC recalled that in the DeLLphi-301 trial 10 mg cohort at the June 2023 data cut-off, adverse events were reported in 97.0% of patients, 29.3% had a treatment-related grade ≥3 adverse event, 58.6% of patients had serious adverse events, and the most commonly reported adverse events were CRS (49.5–90.9%; narrow–broad term), pyrexia (38.4%), constipation (28.3%), anaemia (26.3%), decreased appetite (25.3%), dysgeusia (24.2%), fatigue (21.2%), and asthenia (20.2%).

6.42 All CRS events were Grade 1 or Grade 2 in severity (fever with or without hypoxia or hypotension), most frequently after the first or second dose of tarlatamab, with median time to onset of 13.1 hours and median duration of 4 days. Larger proportions of patients (51.5%) reported CRS events in the DeLLphi-301 10 mg cohort, at the 2 October 2023 data cutoff.

6.43 ICANs and associated neurologic events were reported in 7 (7.1%) patients in the DeLLphi-301 10 mg cohort, most frequently after administration of tarlatamab in Cycle 1, with a median time to onset of 5 days.

Benefits/harms

6.44 On the basis of direct evidence presented in the submission, after a median duration of follow-up of 14 months (April 2025 data cut), for every 100 patients treated with tarlatamab compared to SOC:

- Approximately 17 additional patients would remain alive after 12 months (see Table 4).
- Approximately 14 additional patients would remain progression-free after 12 months (see Table 5).
- Approximately 55 more patients would experience cytokine release syndrome adverse events (see Table 7).
- Approximately 5 more patients would experience ICANS (see Table 7).
- Approximately 30 fewer patients would experience neutropenia (see Table 7).

Clinical claim

6.45 The submission described tarlatamab as superior in terms of effectiveness and safety compared to SOC for the treatment of second-line and subsequent treatment of ES-SCLC in patients who had progressed on or after platinum-based chemotherapy. The ESC agreed with the evaluation that this claim may be reasonable in terms of efficacy, but not safety.

6.46 The following issues should be considered:

- The generalisability of the DeLLphi-304 trial results to the proposed PBS population is unclear, given patients in the trial were required to have an ECOG performance status of 0 or 1 and a minimum life expectancy of 12 weeks, the trial included patients with limited stage disease, and 40% of patients received tarlatamab beyond disease progression (which is inconsistent with the proposed restriction). These differences may result in patients with a poorer prognosis being treated with tarlatamab on the PBS compared to patients in the DeLLphi-304 trial and it is possible that the results of the trial may not be realised in the proposed PBS population.
    - The ESC noted that the PSCR referred to an advisory board which considered that the DeLLphi-304 was applicable to the proposed PBS population and patients in the clinic continuing to second line treatment were relatively fit, much as in the trial, with patients of poor performance status or short life expectancy unlikely to receive further treatment. The ESC agreed with the advisory board advice that only fit patients would be considered for second-line therapy and considered that the generalisability of the trial was likely reasonable. However, the ESC noted that the inclusion of a criterion requiring patients to have a performance status of 0 or 1 in the proposed restriction may be appropriate. The PSCR stated that the advisory board also noted that the treatment effect across different baseline characteristics remained consistent, providing evidence for a consistent effect across differences in populations.

- The PSCR noted that while reported baseline characteristics indicate some DeLLphi-304 patients at the time of screening had limited stage disease, these patients as required by the protocol, had progressed to extensive stage disease by the time of treatment with investigational product.

- Tarlatamab has a different safety profile to SOC chemotherapies. Despite intensive monitoring and dose protocols mandating treatment interruption/discontinuation in the DeLLphi-304 trial, large proportions of patients treated with tarlatamab experienced cytokine release syndrome (narrow: 56.3%; broad: 93.3%) and ICANS (6.0%).
    - The PSCR maintained that the safety profile of tarlatamab was superior compared with SOC chemotherapy. The PSCR stated that an advisory board considered that the safety profile of tarlatamab was predictable and the main side effects were transient given that CRS and ICANs mainly occur during the first 1–2 doses and can be monitored and well-managed. Whereas, chemotherapy-associated toxicities are cumulative, unpredictable, recurrent and persist across cycles. They frequently result in hospitalisation and can be fatal. The PSCR argued that the DeLLphi-304 trial also supports a conclusion of superior safety, given that CRS and ICANs events were mainly mild to moderate in severity. There were less adverse events of grade ≥3 and less treatment modification/interruptions and withdrawals due to adverse event with tarlatamab compared to chemotherapy. The PSCR also argued that the improved tolerability profile was reflected in improved patient reported outcomes from the DeLLphi-304 trial.
    - The ESC considered that due to the high risk of CRS and ICANS, a superior safety claim versus SOC chemotherapy was not well supported. Based on the data available, the ESC considered that the safety profile of tarlatamab was inferior compared to SOC.

6.47 The Pre-PBAC response maintained that the totality of the evidence supported a claim of superior safety and tolerability of tarlatamab compared to SOC chemotherapy. The Pre-PBAC response highlighted that the clinical trial evidence demonstrated that tarlatamab is well tolerated after the initial risk of CRS and ICANS in contrast to chemotherapy which has sustained toxicity. The Pre-PBAC response noted that real-world experience with tarlatamab, as outlined during the hearing and in consumer comments, was also consistent with tarlatamab being better tolerated and demonstrating a superior safety profile compared with SOC chemotherapy. The Pre-PBAC response noted that while tarlatamab represents a new class of therapy in the SCLC setting, bispecific T-cell engagers (BiTEs) are a well-established therapeutic class that have been successfully used in multiple malignancies. The Response stated that appropriate workplace education will be important to ensure optimal identification and management of its safety profile. With adequate training and established

management protocols, CRS and ICANS remain low grade and manageable in clinical practice.

6.48 The PBAC noted that the submission presented the results of the DeLLphi-301 study (02 October 2023 data cut previously considered by the ESC at the March 2025 meeting), as supportive evidence of the efficacy of tarlatamab in third-line and subsequent therapy. The PBAC considered that the efficacy of tarlatamab observed in patients treated with third-line tarlatamab in the DeLLphi-301 study was consistent with the results of the DeLLphi-304 trial, albeit with differing primary endpoints.

6.49 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.50 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data. The PBAC acknowledged that tolerability appeared to improve for tarlatamab patients after the initial risk of CRS and ICANS, however considered that the risk of CRS and ICANS was a substantial safety concern which was likely to have to a large impact in clinical practice, requiring targeted education and considerable healthcare resources to manage appropriately.

Economic analysis

6.51 The submission presented a modelled economic evaluation comparing tarlatamab with topotecan (as a proxy for SOC) for the second-line treatment of ES-SCLC in patients with disease progression on or after platinum-based chemotherapy. Third-line tarlatamab treatment was not modelled in the economic evaluation. The economic evaluation was based on the results of the DeLLphi-304 trial, with additional modelled data. The economic evaluation was presented as a stepped cost-effectiveness/cost-utility analysis.

6.52 Table 8 summarises the key components of the economic evaluation.

Table 8: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Treatments	Tarlatamab versus topotecan as a proxy for SOC
Circumstances of use	Tarlatamab and topotecan treatment regimens were based on the DeLLphi-304 study protocol, Australian product information documents and eviQ treatment protocols. For tarlatamab patients, premedication with dexamethasone and 1-2 hour outpatient monitoring post-infusion were included for the first infusion. This was consistent with the reduced monitoring proposed in the draft PI. Treatment adherence was based on the DeLLphi-304 trial. Duration of therapy was based on time to treatment discontinuation (TTD) curves from the DeLLphi-304 trial extrapolated using standard parametric functions. In the base case, the tarlatamab TTD curve was not adjusted to remove post-progression treatment. A percentage of progressed patients (tarlatamab arm: 67.5%; topotecan: 76.2%) received subsequent treatment (based on the number of patients who received subsequent anticancer therapy in the DeLLphi-304 trial as a proportion of patients with a non-fatal progression event), modelled as a basket of treatments expected to be received in Australian clinical practice (topotecan, carboplatin plus etoposide, CAV).
Outcomes	Quality-adjusted life years; life years

Component	Description
Time horizon	10 years in the base case versus a median follow-up of 14 months for overall survival (29 April 2025 data cut) in the DeLLphi-304 trial.
Cycle length	1 week
Methods used to generate results	Partitioned survival analysis
Health states	Progression-free; progressed disease; dead
Allocation to health states	The allocation of patients to health states was informed by overall survival (OS) and progression-free survival (PFS) curves, with PFS further partitioned into on-treatment and off-treatment using TTD. In the base case, Kaplan-Meier curves for OS, PFS, and TTD were derived from the DeLLphi-304 trial for all patients treated with tarlatamab compared to a subgroup of patients who received topotecan in the comparator arm used as a proxy for standard of care. Kaplan-Meier estimates were used directly in the model until approximately 10% of patients remained at risk in each arm, then extrapolated independently for each treatment arm to 10 years using standard parametric functions (OS using the loglogistic function for tarlatamab and exponential function for topotecan; PFS using the loglogistic function for both treatment arms; TTD using the lognormal function for tarlatamab and exponential function for topotecan). The incidence of Grade 3 or higher adverse events (occurring in at least 5% of patients) and adverse events of special interest for tarlatamab (CRS, ICANS) were included, based on the DeLLphi-304 trial.
Utility values	Health state utilities were estimated based on patient-level EQ-5D-5L data collected in the DeLLphi-304 study (progression-free (tarlatamab): 0.910; progression-free (topotecan): 0.885; progressed-disease: 0.863; based on the Australian value set). Utilities were adjusted for age-related changes and to ensure that utilities did not exceed general population norms based on a survey of a representative sample of Australia's general adult population using the EQ-5D-5L instrument, with estimates reported by age and gender (Redwood 2023). Disutilities associated with Grade 3 or higher adverse events occurring in more than 5% of patients in any treatment arm were included; as well as disutilities for CRS and ICANS events for tarlatamab; based on the published literature and assumption (Nafees 2008; Sullivan 2011).
Costs	Primary and subsequent treatment costs were based on circumstances of use as above, and the proposed DPMA for tarlatamab and published DPMAs/DPMQs for other therapies. Drug administration costs were estimated based on the MBS fee for parenteral administration of one or more antineoplastic agents (#13950). The cost of tarlatamab monitoring on day 1 of cycle 1 was based on reduced monitoring requirements in the draft Product Information (1–2 hours in the outpatient setting) and the cost of chemotherapy treatment (code 10.11, NHCDC 2022-23 Non-admitted Tier 2 v7.0) adjusted to remove pharmacy costs. Disease management costs for patients in the progression-free health states were based on resource use from the NICE atezolizumab submission (TA638) for patients receiving atezolizumab monotherapy after the first 4 chemotherapy cycles, and MBS unit costs. The source of resource use estimates for patients in the progressed disease health state was unclear. Costs associated with Grade 3 or higher adverse events occurring in more than 5% of patients in any treatment arm; as well CRS ($963 per event; assumes 13.4% of events are hospitalised) and ICANS ($177 per event; assumes no events require hospitalisation) all grade events for tarlatamab were included, based on NHCDC Cost weights for AR-DRG v11.0, 2022-23; Public Sector, PBS costs and ICU costs (IHACPA 2025). Terminal care costs ($21,347) were based on health services use in the last month of life in NSW cancer patients (Langton 2016).

Component	Description
	The ESC noted that there were a number of errors and inconsistencies in the costs applied to the economic model, as documented in the evaluation. However, the ESC noted that drug costs were the key driver of differences in costs between arms.
Discounting	5% per year applied to costs and outcomes
Software package	Microsoft Excel

Source: Table 3.1.1-1, p76; and Sections 3.3 to 3.6, pp85-121 of the submission.
Abbreviations: AR-DRG, Australian Refined Diagnosis Related Group; CAV, cyclophosphamide, doxorubicin and vincristine; CRS, cytokine-release syndrome; DPMA, dispensed price for maximum amount; DPMQ, dispensed price for maximum quantity; EQ-5D-5L, EuroQol 5-Dimension 5-Level questionnaire; ICANS, immune effector cell-associated neurotoxicity syndrome; IHACPA, Independent Health and Aged Care Pricing Authority; ICU, intensive care unit; MBS, Medicare Benefits Schedule; NHCDC, National Hospital Cost Data Collection; OS, overall survival; PBS, Pharmaceutical Benefits Scheme; PFS, progression-free survival; PI, product information; SOC, standard of care; TTD, time to treatment discontinuation.

6.53 A partitioned survival approach was used to distribute patients between model health states, with the area below the PFS curve corresponding to patients in the progression-free state, the area between the progression-free and overall survival curves corresponding to patients in the progressive disease health state, and the area above the overall survival curve corresponding to patients in the dead state. The progression-free health state was further partitioned into on- and off-treatment, based on time to TTD curves.

6.54 The base case analysis assumed a 10 year time horizon, on the basis that this corresponds to a lifetime time horizon for the modelled population with a baseline age of 63.9 years. It is unclear whether a 10 year time horizon is appropriate given the uncertainty in the extrapolation of overall survival to 10 years, based on a median follow-up of 14 months from DeLLphi-304. The ESC considered that the time horizon selected for the base case (10 years) was not justified based on the evidence. The ESC noted that the PBAC previously accepted a time horizon in a similar model for atezolizumab in the July 2019 (para 7.12, atezolizumab Public Summary Document [PSD], July 2019 PBAC meeting), but as first-line treatment, of 5 years. The base case for tarlatamab as a second-line treatment should therefore not exceed 5 years. The Pre-PBAC Response maintained that a 10-year time horizon was required to capture the long-term survival benefits of tarlatamab and avoid underestimation of the tarlatamab treatment effect. The Response argued that survival for tarlatamab patients was longer compared to atezolizumab IMpower133 patients, noting that based on the Impower133 trial, at 12 and 18 months approximately 52% and 34% of atezolizumab patients remained alive, respectively, whereas approximately 56.3% and 43.3% of tarlatamab patients remained alive, respectively (data cut-off: 29 April 2025). At 5 years, 16% of DeLLphi-304 patients are still alive. Based on these data, the Response considered tarlatamab had demonstrated improved survival outcomes relative to historical benchmarks, justifying a longer time horizon. However, the PBAC noted that the Response did not provide 5-year OS data for DeLLphi-304 (31 May 2023 [first subject enrolled] to data cut off of 29 April 2025 < 2 years).

6.55 The submission claimed that the modelled population, based on the DeLLphi-304 trial, was consistent with the patient population expected to receive tarlatamab in Australia. However, the evaluation considered that there were differences between

populations which may affect the applicability of the results of the DeLLphi-304 trial, including the performance status of patients, differences in expected life expectancy, and the inclusion of patients with limited-stage disease in the DeLLphi-304 trial. The evaluation considered that the proposed PBS population is likely to have more advanced disease compared to the DeLLphi-304 trial and therefore the clinical benefits seen in the clinical trial (and the economic model) may not be observed in clinical practice (further detailed in paragraph 6.46). The ESC noted that this was a potential applicability issue, however considered that it was likely that only fit patients would be considered for second-line therapy in clinical practice, and the generalisability of the trial was likely reasonable.

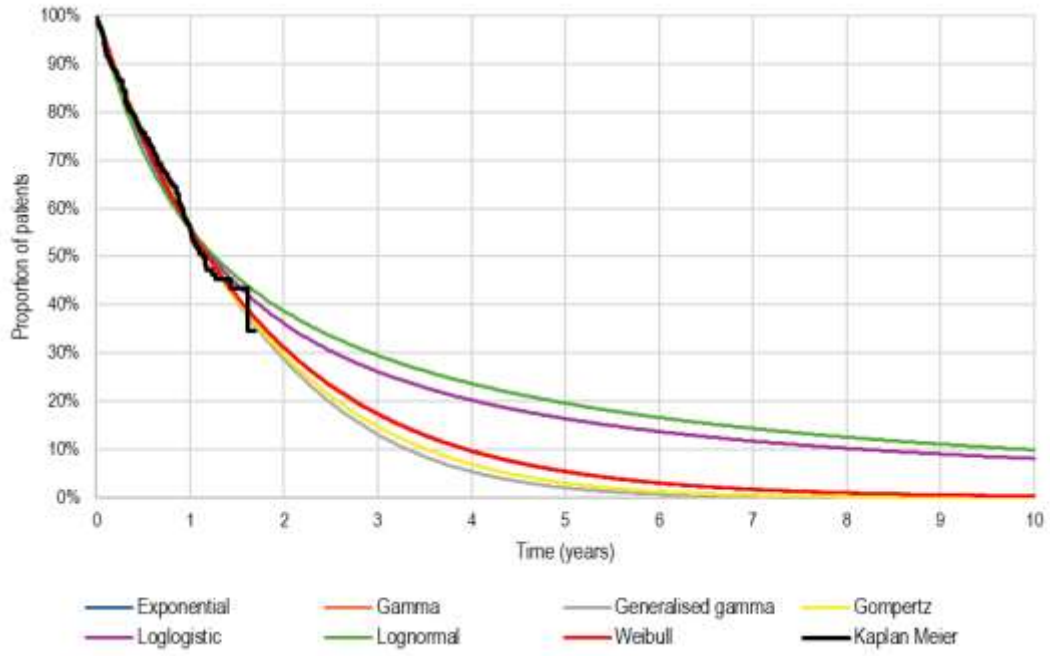
6.56 The DeLLphi-304 trial permitted use of tarlatamab following disease progression if the investigator considered it would be of benefit to the patient, which occurred in 40% of tarlatamab patients with confirmed progression. This was inconsistent with the tarlatamab Product Information which specifies treatment until disease progression or unacceptable toxicity. In the base case of the economic model, OS and TTD for tarlatamab were estimated based on the extrapolated Kaplan-Meier curves without adjustment to remove post-progression use. The submission argued that adjustment was not necessary, as an analysis of overall survival, censored for post-progression treatment, indicated that ongoing use had a limited impact on OS. However, no further documentation was provided in the submission for the adjusted/censored overall survival analysis. The economic model included an option to use the adjusted/censored overall survival data, based on use of parametric functions over the entire time horizon (the Kaplan-Meier data were not included in the model spreadsheet). Overall, the evaluation considered that there was a lack of data to validate the censored/adjusted OS data provided in the model. As detailed in paragraphs 6.15 and 6.16, the PSCR provided additional data related to post-progression use in the DeLLphi-304 trial and also provided the specific rules of the counterfactual adjustment provided in the model. Based on these data, the ESC considered that there was very limited visual evidence of a difference between the OS analyses censored and uncensored for post-progression tarlatamab treatment. The ESC considered that the broader statistical principle of allowing each patient to maximally contribute to the analysis would suggest that the base case should include the adjustment, and that the adjustment appeared reasonable.

6.57 In the base case, TTD in the tarlatamab arm was based on the full trial data (including post-progression tarlatamab treatment), capped at PFS. The submission stated that the cap was applied to align with the tarlatamab Product Information. The economic model also included the option for an 'eventing adjustment' to account for post-progression tarlatamab treatment, however, no details were provided on this adjustment. The ESC noted that the approach to capping the tarlatamab TTD curve to ensure TTD did not exceed PFS, based on a Markov-like approach rather than the standard approach used in partitioned survival analyses likely resulted in a greater reduction in the TTD curve.

6.58 In the model base case, topotecan was used as a proxy for SOC chemotherapies, as the predominant therapy used in the SOC arm of the DeLLphi-304 trial, and a chemotherapy used for second-line and subsequent treatment of ES-SCLC in Australian clinical practice. Overall survival, progression-free survival, time to treatment discontinuation and the incidence of adverse events in the comparator arm of the model were based on the post hoc subgroup of patients in the SOC arm who received topotecan. The submission presented a scenario analysis based on the intention to treat SOC arm of the DeLLphi-304 trial as the comparator arm, however the analysis used the time to treatment discontinuation curve for the topotecan subgroup, which was not justified in the submission.

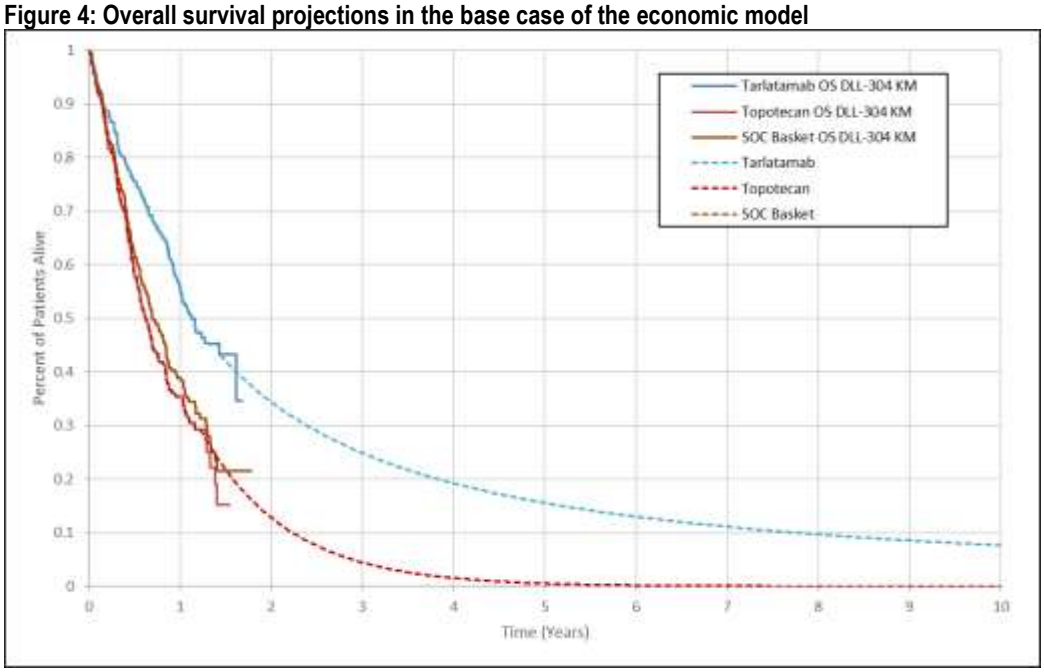
6.59 Figure 3 illustrates the Kaplan-Meier curve and extrapolated parametric functions for overall survival based on the tarlatamab arm of the DeLLphi-304 trial. Figure 4 shows the selected base case projections for OS over the model time horizon.

Figure 3: Parametric extrapolations of overall survival for the tarlatamab arm of the DeLLphi-304 trial



Source: Figure 3.4.2-2, p89 of the submission; 'Tarlatamab 2L CE Model v0.1' model spreadsheet provided with the submission.
Note: The **exponential** and **gamma** curves overlap with the **Weibull** curve and are not visible in the above graph.

Figure 4: Overall survival projections in the base case of the economic model



Source: 'Tarlatamab 2L CE Model v0.1' model spreadsheet provided with the submission

6.60 The best fitting function for the extrapolation of OS in the tarlatamab arm was the exponential function. However, the submission stated that the loglogistic function was selected for the base case based on visual inspection versus the Kaplan-Meier OS curve from the DeLLphi-301 study in third-line therapy (October 2024 data cut). The submission stated that the Kaplan-Meier curve from the DeLLphi-301 study was used as a benchmark of long-term survival, based on the assumption that second-line outcomes would be no worse than those in third-line therapy. Results from the October 2024 data cut of the DeLLphi-301 study were not provided with the submission. The evaluation considered that comparison of the tarlatamab survival curves from the DeLLphi-301 study and DeLLphi-304 trial, conducted in different lines of therapy may not be informative, due to inherent survivorship bias associated with patients who were fit enough to initiate a third-line therapy in the DeLLphi-301 study. The PSCR maintained that the most appropriate extrapolation for tarlatamab OS was the loglogistic function. The PSCR noted that a review of baseline characteristics suggested that the 3L+ population in DeLLphi-301 is not demonstrably fitter or with better survival risk than the 2L+ population in DeLLphi-304 and therefore is useful to inform extrapolation. The PSCR also noted that the latest survival data for tarlatamab, Data snapshot date: 04JUN2025; Data cutoff date: 29APR2025 (DeLLphi-304 median [95% CI] follow up; 13.8 [13.2, 14.7] months) shows hazards of death begin to decrease and flatten slightly which supports a log-based model. The PSCR stated that the use of log-based models is also supported by clinical evidence in immunotherapies, such as

checkpoint inhibitors[2], which suggests there may be a subset of patients with long-term response, therefore outcomes may be best reflected by models with decreasing long-term hazards.

6.61 This ESC noted the goodness-of-fit statistics (Akaike information criterion [AIC], Bayesian information criterion [BIC]) for the parametric functions and the percentages of patients alive at 2.5, 5, 7.5 and 10 years in the economic model based on each parametric function (Table 9 and also shown in Figure 3 and Figure 4). The ESC considered that the loglogistic projections were overly optimistic, particularly given that the OS curves of the two arms did not converge over the 10 year time horizon (Figure 4). The ESC considered that it was more appropriate for the best fitting curve for tarlatamab OS (exponential) to be applied to the base case analysis and noted that this increased the incremental cost-effectiveness ratio (ICER) by [redacted]%. The Pre-PBAC Response maintained that a log-based model would more appropriately capture the expected survival trajectory of tarlatamab patients. The Response reiterated that the hazard of death for tarlatamab is not constant over time with evidence of hazard deceleration. The Response stated that as the exponential model assumes a constant hazard and this structural assumption is not consistent with the observed DeLLphi-304 hazard dynamics and imposes a restrictive structural constraint which underestimates long-term survival. The Response also stated that within the observed trial period, the KM curves showed sustained separation with no evidence of convergence.

Table 9: AIC/BIC statistics and estimated percentages of patients alive at 2.5, 5, 7.5 and 10 years for different parametric functions (DeLLphi-304 tarlatamab arm)

	Exponential	Gamma	Gen. Gamma	Gompertz	Loglogistic	Lognormal	Weibull
TARLATAMAB							
AIC	1,024.6	1,026.6	1,028.3	1,026.5	1,029.6	1,035.0	1,026.6
BIC	1,028.2	1,033.7	1,038.9	1,033.5	1,036.6	1,042.1	1,033.7
Percentage alive							
2.5 years	23.5%	23.4%	19.8%	21.2%	30.5%	33.6%	23.3%
5 years	5.5%	5.5%	2.0%	3.0%	16.4%	19.6%	5.4%
7.5 years	1.3%	1.3%	0.1%	0.3%	10.9%	13.4%	1.2%
10 years	0.3%	0.3%	0.0%	0.0%	8.1%	9.9%	0.3%

Source: Tables 3.4.2-1, p90 and 3.4.2-3, p92 of the submission; 'Tarlatamab 2L CE Model v0.1' model spreadsheet provided with the submission.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; gen., generalised.

6.62 Health state utilities were based on patient-level EQ-5D-5L data from the DeLLphi-304 trial, estimated using generalised estimating equations. Utilities were valued using the Australian value set (Norman 2023). The evaluation considered that the health state utilities derived from patients with relapsed SCLC in the DeLLphi-304 trial (0.885 [topotecan] to 0.910 [tarlatamab] for progression-free disease; 0.863 for progressed

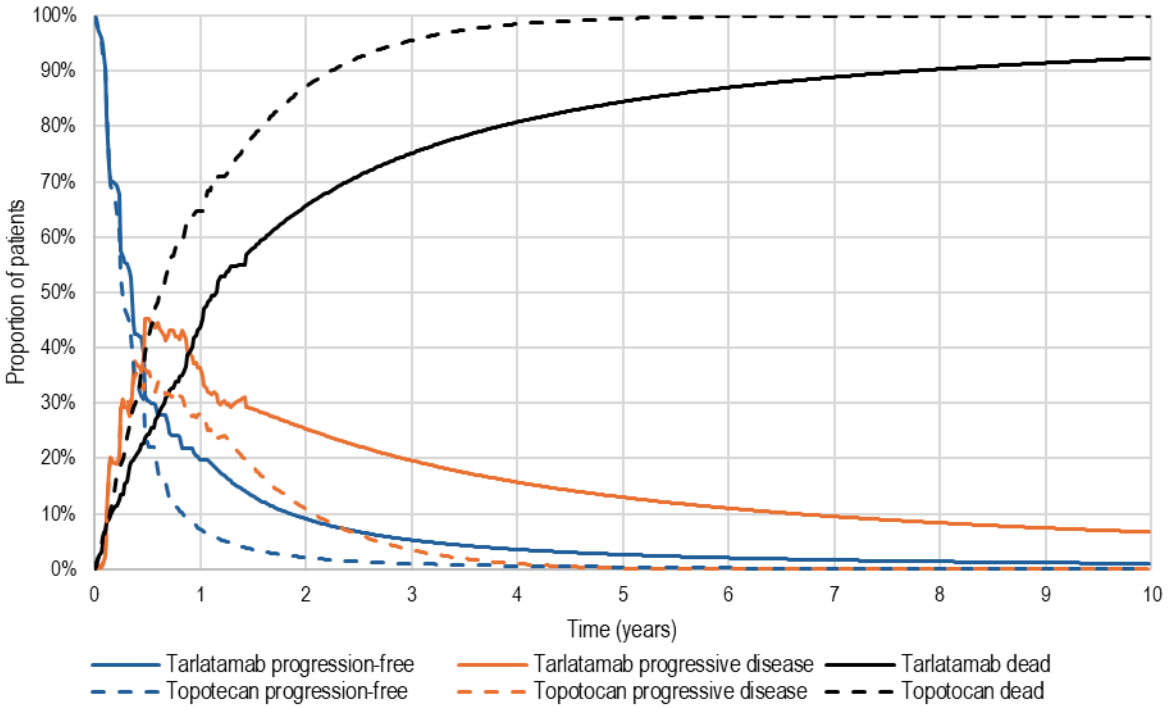
[2] Jedd D. Wolchok et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. *J Clin Oncol* **40**, 127-137(2022).

disease) lacked face validity as they were similar to or higher than Australian general population norms (0.86 to 0.89 for 55 to 64 year olds; McCaffrey 2016, Redwood 2024). Further, given key DeLLphi-304 trial eligibility criteria (ECOG performance status, minimum life expectancy, inclusion of patients with limited stage disease) are not included in the proposed restriction, Australian patients may have a lower quality of life than the DeLLphi-304 trial population. Utilities were also adjusted for age-related changes and to ensure that utilities did not exceed general population norms based on a survey of a sample of Australia's general adult population using the EQ-5D-5L instrument, with estimates reported by age and gender (Redwood 2023). The evaluation considered that age-related utility adjustments were double counted and resulted in higher utilities used over the majority of the model time horizon. The ESC noted that the model included treatment-specific utilities (with a lower utility for the SOC arm than the tarlatamab arm for the progression-free health state). The ESC considered that the use of treatment-specific utilities was not well justified in the submission, particularly given its inferior safety profile. The Pre-PBAC Response stated that treatment-specific utility values for tarlatamab versus topotecan were supported by the trial outcomes and appropriately reflect the overall patient-experienced pre-progression health state. The Response argued that the higher value for tarlatamab was supported by evidence demonstrating improvement to symptomatic disease control, quality of life measures, and also considered that tarlatamab had a superior safety profile compared to SOC chemotherapies.

6.63 The ESC also considered that the utilities were likely too high for this patient group. The ESC also noted that the disutility associated with CRS and ICANS appeared low, however noted this had a limited effect on modelled results. The economic model was sensitive to the use of lower health state utility values. Using alternative utilities (for both arms) for progression-free (0.72) and progressed disease (0.70) increased the ICER by [redacted]%. The ESC noted that the PSCR proposed an alternative utility value for the progression-free health state in the tarlatamab arm, but applied the same decrements as the model base case for SOC treatment and progressed disease and therefore had a limited impact on the economic model.

6.64 Figure 5 presents the model traces for the tarlatamab and topotecan (as a proxy for SOC) arms of the model.

Figure 5: Model traces for the tarlatamab and topotecan (as a proxy for SOC) arms of the model



Source: 'Tarlatamab 2L CE Model v0.1' model spreadsheet provided with the submission.
Abbreviations: SOC, standard of care.

6.65 The model estimated additional survival for tarlatamab of 17.3 months compared with topotecan for the treatment of second-line ES-SCLC. Patients in the tarlatamab arm received an average of 8.9 months of treatment, with an average overall survival of 29.0 months (9.6 months progression-free, and 19.3 months with progressed disease). Patients in the topotecan arm received an average of 4.0 months of treatment, with an average overall survival of 11.6 months (5.2 months progression-free, and 6.5 months with progressed disease).

6.66 Key drivers of the economic model are summarised in Table 10.

Table 10: Key drivers of the economic model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained
Extrapolation of tarlatamab overall survival	The loglogistic function was selected as the base case parametric distribution for tarlatamab overall survival. However, the best fitting function was the exponential curve.	High, favours tarlatamab. Changing the extrapolation of tarlatamab overall survival to the exponential function increased the ICER to $[redacted][2]/QALY gained.
Health state utilities	Progression-free (tarlatamab) 0.910; progression-free (topotecan) 0.885; and progressed-disease 0.863. The health state utilities derived from patients with relapsed SCLC in the DeLLphi-304 trial lack face validity as they are similar to or higher than Australian general population norms. Double counting of age-related utility adjustments resulted in higher utilities used over the majority of the model time horizon.	High, favours tarlatamab. Use of alternative utilities from the July 2019 atezolizumab submission increased the ICER to $[redacted][3]/QALY gained.

Source: Constructed during the evaluation and during the development of the ESC advice.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ICER, incremental cost-effectiveness ratio; SCLC, small cell lung cancer; QALY, quality adjusted life year.
The redacted values correspond to the following ranges:
[1] *$355,000 to < $455,000*
[2] *$655,000 to < $755,000*
[3] *$355,000 to < $455,000*

6.67 The results of the economic evaluation are presented in Table 11 below.

Table 11: Results of the stepped economic evaluation

Step and component	Tarlatamab	SOC	Increment
Step 1: Modelled analysis over 13.8 months based on OS, PFS, and TTD Kaplan-Meier curves for the tarlatamab arm and topotecan SOC subgroup from DeLLphi-304 (PFS and TTD extrapolated using standard parametric functions). Drug, administration and monitoring costs included.			
Costs[a]	$[redacted][a]	$10,028	$[redacted][a]
Life years	0.8526	0.6777	0.1749
Incremental cost per life year gained			$[redacted][1 a]
Step 2: As for Step 1, with time horizon extrapolated to 10 years using standard parametric functions.			
Costs[b]	$[redacted][a]	$10,332	$[redacted][a]
Life years	2.4129	0.9694	1.4434
Incremental cost per life year gained			$[redacted][2 a]
Step 3: As for Step 2, with 5% annual discount rate applied to costs and outcomes.			
Costs[b]	$[redacted][a]	$10,308	$[redacted][a]
Life years	2.1565	0.9451	1.2114
Incremental cost per life year gained			$[redacted][2 a]
Step 4: As for Step 3, with DeLLphi-304 trial-based utilities applied to time spent in the progression-free and progressed disease state.			
Costs[b]	$[redacted][a]	$10,308	$[redacted][a]
QALYs	1.8988	0.8203	1.0785
Incremental cost per life year gained			$[redacted][3 a]
Step 5: As for Step 4, with disease management, subsequent treatment, adverse event and terminal care costs, as well as the disutility associated with adverse events included.			
Costs	$[redacted]	$38,901	$[redacted]
Life years	2.1565	0.9451	1.2114
QALYs	1.8962	0.8155	1.0806
Incremental cost per life year gained			$[redacted][2]
Incremental cost per QALY gained			**$**[redacted][3]

Source: Table 3.9.2-1, p128 of the submission.

Abbreviations: OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time to treatment discontinuation

[a] The submission included an adjustment to monitoring costs based on the tarlatamab TTD curve, which was not included in the model base case and was removed during the evaluation. This had a minor impact on the reported ICER.

[b] Although included in Step 1, the Steps 2 to 4 did not include monitoring costs in the submission. Monitoring costs were included during the evaluation. This had a minor impact on the reported ICERs.

[a] Errors in the cost of tarlatamab, topotecan and third-line SOC chemotherapies were not corrected during the evaluation due to their minimal impact.

The redacted values correspond to the following ranges:

[1] *> $1,055,000*

[2] *$255,000 to < $355,000*

[3] *$355,000 to < $455,000*

6.68 In the model, 86.0% of the incremental QALYs and 37.6% of the incremental costs were accrued in the extrapolated period beyond 14 months.

6.69 For every patient treated with tarlatamab versus topotecan (as a proxy for SOC) and followed for up to 10 years, the economic evaluation (without discounting) estimated that there would be:

- An additional 17.3 months of life lived.
- An additional 4.5 months spent progression-free.
- Additional drug, administration and costs of monitoring of $[redacted]; additional disease management and subsequent therapy costs of $2,942; and reduced adverse event and terminal care costs of $4,615.

6.70 Based on the DeLLphi-304 trial tarlatamab arm and SOC topotecan subgroup, the economic model estimated that treatment with tarlatamab compared to topotecan (as a proxy for SOC) was associated with an incremental cost per quality adjusted life year (QALY) gained of $355,000 to < $455,000.

6.71 The ESC noted that the base case ICER of $355,000 to < $455,000/QALY was substantially higher than previously considered acceptable by the PBAC for ES-SCLC. The PBAC previously considered an ICER of $45,000 to $75,000 per QALY gained acceptable for atezolizumab for induction and maintenance treatment of previously untreated patients with ES-SCLC (para 6.8, atezolizumab PSD, November 2019 PBAC meeting).

The Pre-PBAC Response proposed a revised price for tarlatamab (paragraph 3.2) and base case based on this price (Table 12). The Pre-PBAC Response considered that an ICER of $135,000 to < $155,000 per QALY gained reflected acceptable cost-effectiveness, as tarlatamab is a first-in-class therapy that delivers a survival benefit in a difficult to treat population and in a setting of high clinical need.

Table 12: Results of the economic evaluation base case with revised price

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
Topotecan	$38,901	0.82	$[redacted]	1.08	$[redacted][1]
Tarlatamab	$[redacted]	1.90			

Source: Pre-PBAC Response (p3)
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years
The redacted values correspond to the following ranges:
[1] $135,000 to < $155,000

6.72 The results of key sensitivity analyses included in the submission and conducted during the evaluation are summarised in Table 13.

6.73 The model was most sensitive to the parametric function used to extrapolate tarlatamab overall survival, the price of tarlatamab, tarlatamab treatment adherence, and health state utility values.

Table 13: Results of key sensitivity analyses, based on the submission base case

Analysis	Incremental cost	Incremental QALYs	ICER	% change
Base case of the submission	**$[redacted]**	**1.0806**	**$[redacted][1]**	**-**
Discount rate (base case: 5% costs and outcomes)				
0%	$[redacted]	1.2881	$[redacted]	-[redacted]%
3.5%	$[redacted]	1.1362	$[redacted]	-[redacted]%
Time horizon (base case: 10 years)				
3 years[a]	$[redacted]	0.4703	$[redacted]	+[redacted]%
5 years	$[redacted]	0.7368	$[redacted]	+[redacted]%
7 years	$[redacted]	0.9143	$[redacted]	+[redacted]%
Standard of care arm (base case: topotecan subgroup of the DeLLphi-304 SOC arm used as a proxy for SOC)				
DeLLphi-304 ITT SOC arm[b]	$[redacted]	1.0177	$[redacted][1]	+[redacted]%
Overall survival extrapolation (base case: modelled independently using a loglogistic function for tarlatamab and an exponential function for topotecan)				
Tarlatamab arm based on best fitting exponential function	$[redacted]	0.6007	$[redacted][2]	+[redacted]%
Tarlatamab arm based on the Gompertz function	$[redacted]	0.5045	$[redacted][3]	+[redacted]%

Analysis	Incremental cost	Incremental QALYs	ICER	% change
Base case of the submission	**$[redacted]**	**1.0806**	**$[redacted][1]**	**-**
Topotecan arm based on the gamma function	$[redacted]	1.1194	$[redacted][4]	-[redacted]%
Topotecan arm based on the Weibull function	$[redacted]	1.1309	$[redacted][4]	-[redacted]%
Both arms modelled jointly: exponential function	NR	NR	NR	NR
Both arms modelled jointly: gamma function	$[redacted]	0.5601	$[redacted][2]	+[redacted]%
Both arms modelled jointly: Weibull function	$[redacted]	0.5493	$[redacted][2]	+[redacted]%
Time to treatment discontinuation extrapolation (base case: modelled independently using a lognormal function for tarlatamab and exponential function for topotecan)				
Tarlatamab arm based on the loglogistic function	$[redacted]	1.0806	$[redacted][1]	+[redacted]%
Tarlatamab arm based on the generalised gamma function	$[redacted]	1.0806	$[redacted][1]	+[redacted]%
Topotecan arm based on the gamma function	$[redacted]	1.0806	$[redacted][1]	[redacted]%
Topotecan arm based on the Weibull function	$[redacted]	1.0806	$[redacted][1]	[redacted]%
Impact of capping TTD at PFS based on standard partitioned survival analysis approach[a,c]	$[redacted]	1.0806	$[redacted][1]	+[redacted]%
Utilities (base case: progression-free (tarlatamab) 0.910; progression-free (topotecan) 0.885; progressed disease 0.863; with age-related utility adjustment and population norms as a ceiling)				
Use alternative utilities in the July 2019 atezolizumab submission (progression-free 0.72; progressed disease 0.70) [a]	$[redacted]	0.8806	$[redacted][1]	+[redacted]%
Use progression-free utility in the July 2019 atezolizumab submission (0.72); with decrement for progressed disease from DeLLphi-304 analysis Model 1 (0.035; progressed disease 0.685) [a]	$[redacted]	0.8670	$[redacted][5]	+[redacted]%
Increase tarlatamab relative dose intensity to 100%[a]	$[redacted]	1.0806	$[redacted][4]	-[redacted]%
Decrease tarlatamab relative dose intensity by 20% (75.16%)[a]	$[redacted]	1.0806	$[redacted][1]	+[redacted]%
ESC revised base case				
5 year time horizon; exponential function used to extrapolate tarlatamab OS; health state utilities 0.72 for progression-free, 0.70 for progressed disease	$[redacted]	0.4454	$[redacted][3]	+[redacted]%

Source: Table 3.10.2-1, p131 of the submission; 'Tarlatamab 2L CE Model v0.1' model spreadsheet provided with the submission.
Abbreviations: EMP, ex-manufacturer price; ICER, incremental cost effectiveness ratio; ITT, intention to treat; PFS, progression-free survival; QALY, quality adjusted life year; SOC, standard of care; TTD, time to treatment discontinuation.
[a] Conducted during the evaluation.
[b] The DeLLphi-304 ITT SOC scenario analysis was based on the extrapolated TTD and adverse event incidence of the topotecan subgroup rather than the ITT SOC arm of the DeLLphi-304 trial.
[c] The model implemented a Markov-like approach to ensuring time to treatment discontinuation did not exceed progression-free survival, which multiplied the proportion of patients on treatment in the previous cycle by the risk of treatment discontinuation in the current cycle, capped by progression-free survival.
The redacted values correspond to the following ranges:
[1] *$355,000 to < $455,000*
[2] *$655,000 to < $755,000*
[3] *$755,000 to < $855,000*
[4] *$255,000 to < $355,000*
[5] *$455,000 to < $555,000*

6.74 The ESC considered that the base case ICER was high and uncertain and considered that the projections of the model were overly optimistic, as observed by the lack of convergence of the overall survival curves at ten years. The ESC suggested a revised base case was required to address key uncertainties and unsupported assumptions and included:

- a time horizon of 5 years;
- the exponential (best fitting) extrapolation for OS for the tarlatamab arm; and
- alternative utility values of 0.72 for the progression free and 0.70 for progressed disease.

The ESC noted that these changes increased the ICER to $755,000 to < $855,000/QALY gained (+[redacted]%) and resulted in a life years gained of 0.66 (undiscounted). The ESC recalled it previously considered that it may not be clinically plausible for the health states to have such similar utilities (para 6.49, atezolizumab PSD, July 2019 PBAC Meeting), however considered utility values of 0.72 for the progression free and 0.70 for progressed disease to be more reliable than those applied to the base case analysis. The ESC considered that alternatively the values of 0.72 (progression free) and 0.685 (progressed disease) could also be considered.

Drug cost/patient

6.75 Table 14 presents a comparison of drug costs for tarlatamab and SOC included in the economic model and financial estimates. The financials of the submission assumed a tarlatamab cost per patient per course of $[redacted] for third and subsequent line use (based on a mean duration of treatment of 5.93 months). Third-line tarlatamab treatment was not modelled in the economic evaluation. The Pre-PBAC Response proposed a revised price for tarlatamab (paragraph 3.2). Revised costs per patient per course estimates according to the price proposed in the Pre-PBAC Response is shown below.

Table 14: Drug cost per patient per year for tarlatamab and SOC

	Tarlatamab			SOC		
	Clinical study	Model	Financial estimates	Clinical study	Model	Financial estimates
Second-line (informed by the DeLLphi-304 trial)						
Mean duration of treatment	6.18 months[a]	8.85 months[b]	9.34 months[c]	3.51 months[a]	4.04 months[b]	4.16 months[d]
Cost/patient/ course (submission)	-	$[redacted][e]	$[redacted][f]	-	Topotecan: $7,097[e]	$1,736[e]
Cost/patient/course (Pre-PBAC Response)	-	$[redacted]	$[redacted][g]	-	Topotecan: $7,097[e]	$1,736[e]

Source: 'Tarlatamab 2L CE Model v0.1' model spreadsheet and 'Tarlatamab 2L ES SCLC financial workbook' provided with the submission
Abbreviations: AEMP, approved ex-manufacturer price; CAV, cyclophosphamide + doxorubicin + vincristine; DPMA, dispensed price for maximum quantity; PFS, progression-free survival; SOC, standard of care.
[a] Based on the DeLLphi-304 April 2025 data cut.
[b] Modelled treatment duration based on the extrapolated time to discontinuation curve from the DeLLphi-304 trial, with capping at PFS for the tarlatamab arm.
[c] This 2L estimate could not be verified during the evaluation. Claimed to be based on the second-line tarlatamab modelled treatment duration in error (modelled treatment duration was 8.85 months). The Pre-PBAC Response assumed a mean duration of treatment of 8.85 months.
[d] Claimed to be based on the topotecan modelled treatment duration in error (modelled treatment duration was 4.04 months).
[e] Costing errors identified during the evaluation were not corrected due to the minimal impact.
[f] Calculated as 1 script x weighted DPMQ 1 mg vial ($[redacted]) + 19.83 scripts x weighted DPMQ 10 mg vial ($[redacted])
[g] Calculated as 1 script x weighted DPMQ 1 mg vial ($[redacted]) + 18.87 scripts x weighted DPMQ 10 mg vial ($[redacted])

Estimated PBS usage & financial implications

6.76 This submission was not considered by DUSC.

6.77 The submission used an epidemiological approach to estimate the utilisation and financial impacts of listing tarlatamab for the treatment of patients with ES-SCLC with disease progression on or after platinum-based chemotherapy. The submission used the same approach considered by the DUSC for the withdrawn tarlatamab (third-line) submission intended for the March 2025 PBAC meeting and based on assumptions previously considered by the PBAC in the durvalumab (November 2020 PBAC meeting) and atezolizumab (July 2019 and November 2019 PBAC meetings) submissions.

6.78 Table 15 presents the key inputs relied on in the financial estimates.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incidence of lung cancer in Australia	16,092 in Year 1 (2026), increasing to 17,933 in Year 6 (2031); based on AIHW Cancer Data in Australia 2024.	The DUSC previously considered this source to be reasonable (Table 1, Tarlatamab DUSC Advice, March 2025 PBAC meeting). Updated estimates from the AIHW Cancer Data in Australia 2025 report slightly smaller numbers of expected lung cancer incidence over the same period (15,650 – 17,332).
Percentage of lung cancer that is SCLC	11.75%; based on AIHW 2011 data, assuming a constant percentage over time (reported in the July 2019 atezolizumab and November 2020 durvalumab PSDs).	The DUSC previously considered these estimates to be reasonable (Table 1, Tarlatamab DUSC Advice, March 2025 PBAC meeting).
Percentage of SCLC that is ES-SCLC	92.75%; based on estimates included in the July 2019 atezolizumab and November 2020 durvalumab PSDs (ES-SCLC represents 71.3% of SCLC; 74.75% of LS-SCLC patients, representing 28.7% of SCLC, will progress to ES-SCLC).	
Percentage of ES-SCLC patients receiving 1st line therapy	85%; based on estimates derived from Australian retrospective studies (Ngo 2021: 79%; Huang 2023: 89%).	
Percentage of ES-SCLC 1L patients receiving 2L therapy	45%[a]; based on the percentage of 1L ES-SCLC patients progressing to 2L therapy, reported by Huang 2023 (37%), with a 25% relative increase in the percentage of patients receiving 2L therapy due to tarlatamab's superior efficacy, consistent with the sponsor's advisory board advice.	The ESC noted that the estimate from Huang 2023 could not be verified during the evaluation. Ngo 2021 reported 29% of patients with SCLC received 2L therapy. The 25% relative increase in the proportion of patients receiving 2L therapy could not be verified during the evaluation. The advisory board advice was not provided. The Pre-PBAC Response applied a percentage of 40%; stated to be based on the estimate from Huang 2023 (37%) and a 10% relative increase (rounded down).
Percentage of ES-SCLC 2L patients receiving 3L therapy	38%; based on the percentage of 1L patients estimated to receive 3L therapy in the withdrawn tarlatamab submission (17.5%, derived from a survey of Australian experts who estimated that 58% of 1L patients would receive 2L, and 24% of 2L patients would receive 3L, with a 25% relative increase in the percentage of 1L patients who would proceed to 3L therapy. Applied to the percentage of patients not receiving 2L tarlatamab).	The ESC noted that the DUSC previously considered the estimate of 17.5% of 1L patients receiving 3L therapy, the basis of this calculation, to be reasonable. The ESC considered that assuming 38% was likely an overestimate. The Pre-PBAC Response stated that the relative increase of 25% was reduced to 10%. However, the workbook provided with the Response applied 38% (assumed to include a 25% relative increase; calculations for estimate was not provided).
Uptake in the 2L and 3L settings	[redacted]% in Year 1, increasing to [redacted]% in Years 3-6; assumed.	The evaluation considered that the uptake of tarlatamab is assumed, and highly uncertain.
Tarlatamab treatment duration (10 mg)	2L: 9.34 months; based on the mean 2L treatment duration estimated in the economic model, derived	The ESC noted that the 2L estimate could not be verified during the evaluation (mean treatment duration from the economic model

Parameter	Value applied and source	Comment
	from the extrapolated TTD curve for the tarlatamab arm of the DeLLphi-304 trial. 3L: 5.93 months; based on the mean 3L treatment duration estimated in the economic model presented in the withdrawn 3L tarlatamab submission, based on the extrapolated TTD curve from the DeLLphi-301 study, censored for post-progression treatment removing the last remaining 10% of patients.	was 8.85 months). The Pre-PBAC Response updated the financial estimates with an estimate of 8.85 months. It is uncertain whether the duration of therapy derived from the DeLLphi-304 trial will be realised in the Australian clinical setting. The TTD curve used in the model base case included use of tarlatamab post-progression, with TTD capped at PFS. For 3L, the ESC noted that removing the last remaining 10% of patients from the entire TTD curve was not appropriate. As a result the TTD for 3L was likely underestimated.
SOC treatment duration	2L: 4.16 months; based on the mean 2L treatment duration estimated in the economic model, derived from the extrapolated TTD curve for the topotecan SOC subgroup of the DeLLphi-304 trial. 3L: 1.80 months; based on the mean 3L treatment duration estimated in the economic model presented in the withdrawn 3L tarlatamab submission, based on the extrapolated TTD curve from the CAS SOC cohort, removing the last remaining 10% of patients.	The 2L estimate could not be verified during the evaluation (mean treatment duration from the economic model was 4.04 months). It is uncertain whether the duration of therapy derived from the topotecan post hoc subgroup from the DeLLphi-304 trial will be realised in the Australian clinical setting. DUSC previously considered the 3L estimate to be reasonable (Table 1, Tarlatamab DUSC Advice, March 2025 PBAC meeting). For 3L, the ESC noted that removing the last remaining 10% of patients from the entire TTD curve was not appropriate. As a result the TTD for 3L was likely underestimated.
Distribution of SOC therapies	2L: topotecan 30%, carboplatin+etoposide 40%, CAV 30%; assumed. Adjusted to account for 20% of patients who would otherwise not be treated if tarlatamab was not available. 3L: topotecan 42%, carboplatin + etoposide 21%, CAV 37%; based on the proportion of use in the CAS 2023 study. Adjusted to account for 20% of patients who would otherwise not be treated if tarlatamab was not available.	The estimated distribution of 2L SOC therapy use and additional proportion of patients who would be treated if tarlatamab is listed were assumed and highly uncertain.

Source: Table 4.1.1-1, p135 of the submission.

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; AIHW, Australian Institute of Health and Welfare; CAS, Cancer Analysis System; CAV, cyclophosphamide + doxorubicin + vincristine; DUSC, Drug Utilisation Sub Committee; ES-SCLC, extensive-stage small cell lung cancer; LS-SCLC, limited-stage small cell lung cancer; PBAC, Pharmaceutical Benefits Advisory Committee; PFS, progression-free survival; PSD, Public Summary Document; SCLC, small cell lung cancer; SOC, standard of care; TTD, time to treatment discontinuation.

[a] It was noted during the evaluation that 37%×1.25=46.25%. The value used in the submission (45%) may be the result of rounding. This impacted the calculation for SOC substitution by tarlatamab in the 2L setting [37%÷46.25%=80%].

6.79 The ESC noted that the estimated net costs to the PBS/RPBS of listing tarlatamab were uncertain, based on the assumption that the availability of tarlatamab would increase the proportion of ES-SCLC patients initiating second-line and third-line therapy by 25%, highly uncertain, uptake rates ([redacted]% to [redacted]%), and estimates of average duration of therapy and relative dose intensity that could not be verified during the evaluation. The ESC considered that the projected increase in patients initiating second- and third-

line therapy following the introduction of tarlatamab to be highly uncertain. Given the relatively poor fitness of the patient group, it is possible that no increase would occur. However, the ESC considered that there may be a small percentage, possibly an additional 10%, of patients that may initiate tarlatamab, who otherwise would have chosen not to receive additional chemotherapy. The Pre-PBAC Response reduced the projected increase in the percentage of patients initiating second-line therapy following the introduction of tarlatamab from 25% to 10%. The Pre-PBAC Response also revised second-line treatment duration from 9.53 to 8.85 months consistent with the economic model.

6.80 In addition, the ESC noted that there is a high risk of use outside the proposed restriction, including the treatment of patients with LS-SCLC (included in the proposed TGA indication), and continuing treatment of patients after disease progression (which occurred in 40% of patients with disease progression in the key DeLLphi-304 trial). The PSCR noted that an advisory board indicated that there is a clear delineation between LS and ES SCLC and noted the current lack of tarlatamab data in the LS-SCLC setting. Consequently, the advisory board were of the view that there would be limited risk of use outside a PBS restriction which specifies ES-SCLC. However, the PSCR acknowledged there was a risk of use beyond progression. The PSCR considered that continuation of treatment beyond progression is expected to be limited to select patients with ongoing clinical benefit, most commonly in the setting of isolated or oligoprogression amenable to local therapy. The PSCR noted that the proposed treatment duration used in the financial analysis reflects treatment until progression and noted the sponsor was willing to adopt a risk sharing arrangement to manage the risk of treatment beyond that projected in the financial estimates.

6.81 Table 16 summarises the estimated use and financial implications of listing tarlatamab on the PBS/RPBS. Although the submission proposed grandfathering provisions in the requested restriction, the submission did not include grandfathered patients in utilisation estimates. The Pre-PBAC Response proposed a revised price for tarlatamab (paragraph 3.2). The updated financial estimates, based on the Pre-PBAC Response, are shown in Table 16.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Incident patients with SCLC	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Patients treated with 2L tarlatamab	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Patients treated with 3L tarlatamab	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total tarlatamab 1 mg scripts[a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total tarlatamab 10 mg scripts[b]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Submission:						
Estimated financial implications of tarlatamab						
Cost to PBS/RPBS less copay.	$[redacted][4]	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Estimated financial implications of SOC						
Cost to PBS/RPBS less copay.	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]
Net financial implications						
Net cost to PBS/RPBS	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][5]**
Total cost to MBS[c]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
Net cost to PBS/RPBS/MBS	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][5]**
Pre-PBAC Response:						
Estimated extent of use						
Patients treated with 2L tarlatamab	[redacted][2]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Patients treated with 3L tarlatamab	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of tarlatamab						
Cost to PBS/RPBS less copay.	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]
Estimated financial implications of SOC						
Cost to PBS/RPBS less copay.	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]
Net financial implications						
Net cost to PBS/RPBS	**$[redacted][8]**	**$[redacted][9]**	**$[redacted][9]**	**$[redacted][9]**	**$[redacted][9]**	**$[redacted][9]**
Total cost to MBS[c]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
Net cost to PBS/RPBS/MBS	**$[redacted][8]**	**$[redacted][9]**	**$[redacted][9]**	**$[redacted][9]**	**$[redacted][9]**	**$[redacted][9]**

Source: Attachment 14 - Tarlatamab ES-SCLC Financial Model provided with the submission. Pre-PBAC Response (p3 and attached workbook).

Abbreviations: 2L, second-line; 3L, third-line; copay., copayments; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme; SOC, standard of care.

[a] 1×1 mg script per patient.

[b] 19.83×10 mg scripts per patient in the second-line setting; 11.76×10 mg scripts per patient in the third-line setting.

[c] Increased administration costs associated with tarlatamab due to the increased second- and third-line treated population and longer duration of therapy; based on MBS item 13950 ($100.80, derived from them MBS fee of $126.00, assuming an 80% rebate).

Note: Discrepancies between estimates in the submission and budget impact model spreadsheet were identified during the evaluation.

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] < 500

[3] 10,000 to < 20,000

[4] $200 million to < $300 million

[5] $300 million to < $400 million

[6] net cost saving

[7] $0 to < $10 million

[8] $90 million to < $100 million

[9] $100 million to < $200 million

6.82 Based on the revised estimates provided in the Pre-PBAC Response the estimated net cost to the PBS/RPBS of listing tarlatamab was $90 million to < $100 million in Year 1,

increasing to $100 million to < $200 million in Year 6, a total cost of $600 million to < $700 million over the first 6 years of listing.

Quality Use of Medicines

6.83 The submission noted planned support and education activities designed to ensure the safe and effective use of tarlatamab, including: developing educational resources to assist healthcare providers in identifying eligible patients and ensuring informed decision-making based on therapeutic guidelines, working with eviQ and clinical centres to develop guidelines and protocols, working with clinical sites to develop site-specific treatment protocols, including detailed guidance on monitoring for managing CRS and ICANS, and accreditation programs will be established to ensure prescribers are sufficiently trained in managing the administration of tarlatamab and associated risks.

Financial Management – Risk Sharing Arrangements

6.84 The PSCR noted that the proposed treatment duration for tarlatamab used in the financial analysis reflects treatment until progression however acknowledged there was a risk of use beyond progression. The sponsor noted it was willing to adopt a risk sharing arrangement to manage the risk of treatment beyond that projected in the financial estimates.

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

7 PBAC Outcome

7.1 The PBAC did not recommend tarlatamab for the treatment of extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after first line treatment with platinum-based chemotherapy. The PBAC noted there is a high clinical need as ES-SCLC is a rapidly progressive disease and there are limited effective treatments in the second- and later-line settings. The PBAC noted that the trial evidence suggested that tarlatamab was associated with benefits in terms of progression free survival (PFS) and overall survival (OS) compared to standard of care (SOC) chemotherapy but noted that tarlatamab was associated with a high risk of life-threatening immune effector cell-associated neurotoxicity syndrome (ICANs) and cytokine release syndrome (CRS). The PBAC agreed with the ESC that revision to the economic model was required to address key uncertainties. The PBAC noted that incorporating the ESC's recommended revisions, together with the price proposed in the pre-PBAC Response, resulted in an unacceptably high incremental cost-effectiveness ratio (ICER). The PBAC considered that a price reduction would be required to achieve a cost-effective listing, together with a risk sharing arrangement (RSA) to mitigate the risk of use outside the proposed restriction. The PBAC advised that the remaining issues could be addressed in an early re-entry submission.

7.2 The PBAC considered that the primary reason for this outcome was the economic

evaluation.

7.3 The PBAC noted and welcomed comments from health care professionals, individuals who would like access to tarlatamab, and medical/consumer organisations. The PBAC noted comments highlighting that there was currently a high clinical need for effective therapies for ES-SCLC, noting that patients currently have few effective treatment options, with only modest clinical benefit, and typically face rapidly progressive disease, substantial symptom burden, and short survival. The PBAC noted that comments acknowledged that the adverse events associated with tarlatamab would necessitate access to acute toxicity management and supporting infrastructure, which could lead to cost and implementation challenges in routine Australian practice. However, the comments stated that overall tarlatamab remained better tolerated than SOC chemotherapy, with side effects commonly only occurring early in the treatment process, making them more predictable compared to current treatment options which are cumulative and ongoing.

7.4 The PBAC noted that the proposed clinical place for tarlatamab was for the treatment of patients with ES-SCLC with disease progression on or after first line treatment with platinum-based chemotherapy (i.e. second-line or subsequent treatment). The PBAC considered that this was appropriate.

7.5 With respect to the proposed restrictions, the PBAC proposed the following:

- A Section 100, Efficient Funding of Chemotherapy (EFC) Authority required (STREAMLINED) listing was appropriate for the initial, continuing and grandfather treatment phases. The initial treatment restriction should have 0 repeats with 6 repeats for continuing and grandfathering treatment phases.
- Medical practitioners should be the sole prescriber type.
- Limiting treatment to ES-SCLC was reasonable (paragraph 3.3).
- The proposed stopping rule (disease progression) was reasonable (paragraph 3.4).
- The criterion requiring patients to have progressed on or after platinum-based chemotherapy (PBC) and does not allow access to patients with a clinical contraindication or intolerance to PBC was appropriate (paragraph 3.5).
- The prescribing instruction outlining monitoring requirements should be consistent with the current TGA approved Product Information (PI), i.e. 'Monitor patients from the start of the infusion for 16 hours on Cycle 1 Day 1 in an appropriate healthcare setting', and agreed with the submission that a hospital is the best placed setting in this circumstance (paragraph 3.6).
- Inclusion of a criterion requiring patients to have a performance status of 0 or 1 was not required (paragraph 3.7).
- The grandfather listing should allow patients who had previously received treatment via compassionate access means, to be able to bypass the monitoring

requirements required during the first treatment cycle (paragraph 3.9).

7.6 The submission nominated SOC chemotherapies as the main comparator. Topotecan was proposed as a proxy for SOC given it is available and widely used in Australia. The PBAC considered that this was reasonable.

7.7 The PBAC noted that the submission was based on a head-to-head phase 3, open-label, randomised controlled trial comparing tarlatamab to SOC chemotherapy (topotecan, lurbinectedin, amrubicin) in SCLC patients with disease progression or recurrence following a platinum-based regimen (DeLLphi-304). The PBAC noted a majority of patients received topotecan. The PBAC noted that based on a median follow up of 11.2 months in the tarlatamab arm and 11.7 months in the SOC chemotherapy arm, tarlatamab was associated with a moderate and statistically significant improvement in OS compared to SOC (median 13.6 versus 8.3 months, hazard ratio [HR]: 0.599; 95% confidence interval [CI]: 0.468, 0.768). The PBAC noted that based on a median follow up of 11.0 months in the tarlatamab arm and 9.7 months in the SOC chemotherapy arm, tarlatamab was associated with a small but statistically significant improvement in PFS compared with SOC (median 4.2 versus 3.2 months, HR: 0.72; 95% CI: 0.59, 0.88). The PBAC noted that the DeLLphi-304 trial had a high risk of bias due to its open-label design, which may have influenced clinical management and investigator-assessed outcomes. The PBAC noted that the trial population appeared to have a more favourable baseline prognosis than the patient population proposed for the PBS. Patients in the trial were required to have an ECOG performance status of 0 or 1 and a minimum life expectancy of 12 weeks, the trial included patients with limited stage disease, and 40% of patients received tarlatamab beyond disease progression (which is inconsistent with the proposed restriction). Overall, the PBAC considered that the claim of superior comparative effectiveness compared to SOC chemotherapy was reasonable.

7.8 The PBAC noted that higher percentages of patients in the tarlatamab arm compared to the SOC arm of the DeLLphi-304 trial experienced CRS (narrow definition: 56.3% versus 1.2%; broad definition: 93.3% versus 85.2%) and neurological events (55.6% versus 35.2%), including ICANS (6.0% versus 0.8%). The PBAC acknowledged the Pre-PBAC Response highlighting that the clinical trial evidence demonstrated that tarlatamab is well tolerated after the initial risk of CRS and ICANS in contrast to chemotherapy which has sustained and cumulative toxicity. The PBAC considered that while tolerability appeared to improve for tarlatamab patients after the initial risk of CRS and ICANS, the high risk of CRS and ICANS was a substantial safety concern which was likely to have to a large impact in clinical practice, requiring targeted education and considerable healthcare resources to manage appropriately. For this reason, the PBAC considered that the claim of superior comparative safety was not adequately supported by the data.

7.9 The PBAC noted that the submission presented the results of the DeLLphi-301 study (02 October 2023 data cut previously considered by the ESC at the March 2025 meeting), as supportive evidence of the efficacy of tarlatamab in third-line and

subsequent therapy. The PBAC noted that the submission referred to an October 2024 data cut for the DeLLphi-301 study, but these data were not provided with the submission. The PBAC considered that the efficacy of tarlatamab observed in patients treated with third-line tarlatamab in the DeLLphi-301 study was consistent with the results of the DeLLphi-304 trial.

7.10 The PBAC noted the submission presented a cost-utility analysis to support the cost-effectiveness of tarlatamab versus topotecan (as a proxy for SOC) for the second-line treatment of ES-SCLC in patients with disease progression on or after PBC. Third-line tarlatamab treatment was not modelled in the economic evaluation. The PBAC acknowledged the key concerns raised by the ESC (paragraph 6.74). The PBAC noted that the ESC considered that the time horizon selected for the base case (10 years) was not justified based on the evidence. The PBAC considered the supporting arguments provided in the Pre-PBAC Response for a 10 year time horizon (paragraph 6.54) did not adequately justify extending the time horizon and agreed with the ESC that a 5 year time horizon remained appropriate for this patient group. The PBAC noted that the ESC also considered that the best fitting curve for tarlatamab OS (exponential) should be applied to the base case analysis. The PBAC agreed with the ESC that the assumption of substantial and sustained separation of OS curves, without convergence, was highly uncertain and likely to be overly optimistic, particularly given that observed data were only available up to a median of 14 months for OS (29 April 2025 data cut) in the DeLLphi-304 trial. The PBAC noted that more mature OS data from DeLLphi-304 is anticipated in April 2026, which would provide an additional 12 months of follow-up data. The PBAC considered that these data may provide an important basis for informing model extrapolations and validating long-term OS projections.

7.11 The PBAC also considered that the health state utilities derived from patients in the DeLLphi-304 trial lacked face validity as they are similar to or higher than Australian general population norms and noted that double counting of age-related utility adjustments resulted in higher utilities used over the majority of the model time horizon. The PBAC considered that the use of alternative utility values of 0.72 for progression free and 0.70 for progressed disease would be appropriate and consistent with the July 2019 atezolizumab submission.

7.12 The PBAC noted that when inputs were adjusted according to the ESC advice (as noted above), together with the price proposed in the Pre-PBAC Response, the ICER was $255,000 to < $355,000 per quality adjusted life year (QALY) gained. The PBAC considered that this ICER was unacceptably high and that tarlatamab was not cost-effective at the price proposed in the Pre-PBAC Response. The PBAC recalled that it had previously considered an ICER of $45,000 to $75,000 per QALY gained acceptable for ES-SCLC. The PBAC considered that a substantial price reduction would be required for tarlatamab to achieve a cost-effective PBS listing. The PBAC considered that more mature OS data from DeLLphi-304 may provide an important basis for informing the model extrapolations and validating long-term OS projections.

7.13 The PBAC noted that the Pre-PBAC Response provided revised financial estimates incorporating a revised price and additional amendments in line with the ESC advice. The PBAC noted that some errors remained in the calculations for the eligible patient population, including for the percentage of ES-SCLC second-line patients receiving third-line therapy (incorrect percentage increase) and third-line treatment duration (incorrect data censoring; see Table 15). The PBAC considered that, with corrections to these errors and with the price reduction required to achieve cost effectiveness as outlined in paragraph 7.12, it would be reasonable to accept the Pre-PBAC Response revised financial estimates as the basis of establishing a risk sharing arrangement (RSA).

7.14 The PBAC considered that there was a risk that tarlatamab would be used outside of the proposed patient population in patients with LS-SCLC (included in the proposed TGA indication) and as continuing treatment of patients after disease progression. The PBAC considered that the risk of use outside the proposed restriction and the remaining uncertainties in the financial estimates could be managed through an RSA.

7.15 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for tarlatamab using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:

- A revised restriction that includes changes outlined in paragraph 7.5;
- A revised economic model, which includes changes, in line with the ESC advice, related to the time horizon, tarlatamab OS extrapolation, and utility values, as outlined in paragraphs 7.10 and 7.11;
- A pricing proposal that results in an ICER no greater than $75,000 per QALY gained;
- Revised financial estimates which includes corrections to errors outlined in paragraph 7.13 and a reduced tarlatamab price; and
- A proposed RSA (see paragraph 7.14).

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

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

Outcome:
Not recommended

8 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.

9 Sponsor's Comment

The sponsor had no comment.

Addendum to the March 2026 PBAC PSD

3.04 TARLATAMAB, Powder for injection 1 mg, Powder for injection 10 mg, Imdelltra®, Amgen Australia Pty Ltd

10 Purpose

10.1 To reconsider whether tarlatamab for the treatment of extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after first line treatment of platinum-based chemotherapy meets the 'high added therapeutic value' (HATV) criteria: (i) addresses a high and urgent unmet clinical need and (ii) provides a substantial and clinically relevant improvement in efficacy, or reduction in toxicity, over any alternative therapy.

11 Background

11.1 At its March 2026 meeting, the PBAC did not recommend tarlatamab for the treatment of ES-SCLC with disease progression on or after first line treatment of platinum-based chemotherapy.

11.2 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission using the early re-entry pathway, rather than an early resolution pathway which requires a medicine to meet the HATV criteria (paragraph 7.15).

11.3 The sponsor requested the PBAC reconsider if tarlatamab meets the HATV criteria.

12 PBAC Outcome

12.1 The PBAC provided additional advice for tarlatamab, for the treatment of extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after first line treatment of platinum-based chemotherapy, previously considered at the March 2026 PBAC Meeting. The PBAC considered that for this patient population, tarlatamab met the 'high added therapeutic value' (HATV) criteria as it addressed a high and urgent unmet clinical need and provided a substantial and clinically relevant improvement in efficacy compared to standard of care (SOC) chemotherapies.

12.2 The PBAC maintained that the outstanding issues related to the tarlatamab submission considered at the March 2026 PBAC Meeting could be resolved in a simple resubmission for tarlatamab. Given the PBAC considered that tarlatamab is of high added therapeutic value, the PBAC considered an early resolution resubmission pathway would be appropriate.

12.3 The PBAC advised that if the sponsor accepts the early resolution resubmission pathway, the changes to address outstanding issues without requiring further re-evaluation, remain unchanged from that previously advised (as stated in paragraph 7.15).

12.4 If the issues cannot be addressed by the sponsor in a simple resubmission a standard re-entry pathway is available.

Outcome:
Advice provided

13 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.

14 Sponsor's Comment

The sponsor had no comment.