Canadian Journal of Health Technologies

Canada's Drug Agency
L'Agence des médicaments du Canada

March 2025 Volume 5 Issue 3

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Tarlatamab (Imdelltra)

Indication: The treatment of adult patients with extensive-stage small cell lung cancer with disease progression on or after at least 2 prior lines of therapy including platinum-based chemotherapy

Sponsor: Amgen Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Imdelltra?

Canada's Drug Agency (CDA-AMC) recommends that Imdelltra be reimbursed by public drug plans for the treatment of extensive-stage small cell lung cancer (ES-SCLC) in patients with disease progression on or after at least 2 prior lines of therapy including platinum-based chemotherapy if certain conditions are met.

Which Patients Are Eligible for Coverage?

Imdelltra should only be covered to treat adult patients who have relapsed or refractory small cell lung cancer (SCLC), have received 2 or more lines of previous therapies (including 1 chemotherapy containing platinum and at least 1 other therapy), and who are in relatively good health. Imdelltra should not be covered for patients with untreated or symptomatic brain metastases.

What Are the Conditions for Reimbursement?

Imdelltra should only be reimbursed if administered in centres with appropriate medical support to manage potentially life-threatening adverse events, such as cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS), and if the cost of Imdelltra is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that treatment with Imdelltra caused tumours to shrink on imaging. However, it was uncertain whether treatment with Imdelltra could extend life or increase the time until the cancer grows or spreads because Imdelltra was not compared to any other drugs.
- Imdelltra may meet some important patient needs by offering an additional treatment option that could result in a durable treatment response.
- Based on the CDA-AMC assessment of the health economic evidence, Imdelltra does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Imdelltra is estimated to cost the public drug plans approximately $33.2 million over the next 3 years, but the actual budget impact is uncertain. Imdelltra also requires the first 2 doses to be administered in a hospital inpatient setting and may require additional days of hospitalization for patients with CRS and ICANS adverse events

Summary

(AEs). These additional costs were not considered within the budget impact analysis (BIA).

Additional Information

What Is SCLC?

SCLC is a fast-growing type of cancer that starts in the lungs and accounts for 10% to 15% of all lung cancer cases. Approximately two-thirds of SCLC diagnoses are classified as ES-SCLC, which is characterized by widespread tumour involvement in the lungs, metastases, and poor prognosis; most patients with ES-SCLC live for less than 1 year.

Unmet Needs in ES-SCLC

Although most patients with ES-SCLC respond to first-line treatment with chemotherapy, many patients relapse within months and are not well enough to receive second-line chemotherapy. There is a need for new, life-extending treatments with minimal side effects that improve quality of life.

How Much Does Imdelltra Cost?

Based on public list prices, treatment with Imdelltra is expected to cost approximately $32,445 per patient for the first 28-day cycle and $30,900 per patient for each subsequent 28-day treatment cycle.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that tarlatamab be reimbursed for the treatment of adult patients with ES-SCLC with disease progression on or after at least 2 prior lines of therapy including platinum-based chemotherapy, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 ongoing phase II, open-label, single-arm study (DeLLphi-301; N [Part 1 and 2] = 99) in adult patients (≥ 18 years) with ES-SCLC with disease progression on or after at least 2 prior lines of therapy (including 1 platinum-based chemotherapy) demonstrated that treatment with tarlatamab may result in a clinically meaningful benefit in overall response rate (ORR) (41.4%; 97.5% confidence interval [CI], 30.3% to 53.2%). However, the effect of tarlatamab on overall survival (OS) (median = 14.3 months; 95% CI, 10.8 months to not estimable [NE]) and progression-free survival (PFS) (median = 4.3 months; 95% CI, 3.0 to 5.6 months) was uncertain due to the single-arm study design.

There is a lack of direct comparative evidence for tarlatamab compared to other treatments for ES-SCLC. As such, comparative evidence available for this review was based on several sponsor-submitted indirect treatment comparisons (ITCs) (propensity score weighting and matching-adjusted indirect comparisons [MAICs]), which evaluated the efficacy of tarlatamab versus comparator treatments in the third-line or beyond setting. Overall, the ITCs had several important limitations, including heterogeneity in patient populations and study design and a high risk of selection bias. Therefore, pERC could not draw conclusions on the comparative efficacy or safety of tarlatamab in the third-line setting.

pERC noted that there is an important unmet need for additional treatment options in this patient population because of the poor prognosis with ES-SCLC and the lack of funded, effective therapies in the third-line or beyond setting. Patients identified a need for novel, additional treatment options that delay disease progression, prolong survival, control disease symptoms, improve or maintain HRQoL, and reduce side effects. pERC acknowledged that tarlatamab may provide an additional treatment option that results in a response that appears durable in a heavily pretreated population as in the DeLLphi-301 trial. However, pERC could not conclude that a response to treatment would result in a meaningful delay in disease progression or improved survival. In addition, pERC could not conclude that tarlatamab resulted in improved HRQoL due to the results being based on a small subset of patients in the DeLLphi-301 trial. It is also uncertain whether tarlatamab was associated with a more favourable side effect profile than other treatments because this was not evaluated in the ITCs provided.

Using the sponsor-submitted price for tarlatamab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for tarlatamab was $559,946 per quality-adjusted life-year (QALY) gained compared with a basket comparator (consisting of topotecan; combination therapy of a platinum agent and etoposide; combination therapy of cyclophosphamide, doxorubicin, and vincristine (CAV); etoposide; and irinotecan). At this ICER, tarlatamab is not cost-effective at a willingness-to-pay threshold of

$50,000 per QALY gained for adult patients with ES-SCLC after platinum-based chemotherapy and at least 1 other treatment. A price reduction is required for tarlatamab to be considered cost-effective at a threshold of $50,000 per QALY gained.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with tarlatamab should be reimbursed when initiated in adult patients (≥ 18 years) who: 1.1. have relapsed or refractory SCLC 1.2. have received 2 or more lines of therapy, including 1 platinum-based regimen and at least 1 other prior line of therapy.	In the DeLLphi-301 trial, treatment with tarlatamab demonstrated a clinical benefit in patients with relapsed or refractory SCLC who previously received 2 prior lines of therapy, including 1 platinum-based regimen.	—
2. Patients must have a good performance status.	Patients with an ECOG performance status of 0 or 1 were included in the DeLLphi-301 trial.	Patients with an ECOG performance status of 2 may be treated at the discretion of the treating clinician.
3. Patients must not have untreated brain metastases.	The DeLLphi-301 trial excluded patients with untreated or symptomatic brain metastasis and leptomeningeal disease. As such, the potential benefit of tarlatamab in these patients has not been demonstrated.	Patients with treated or stable CNS metastases should be eligible for treatment.
Discontinuation		
4. Treatment should be discontinued upon the occurrence of either of the following: 4.1. clinical disease progression 4.2. unacceptable toxicity.	Patients in DeLLphi-301 discontinued treatment upon progression or unacceptable toxicity, consistent with clinical practice.	—
Prescribing		
5. Tarlatamab should only be administered in centres with appropriate medical support to manage potentially life-threatening adverse events, such as CRS and ICANS.	This condition is to ensure that treatment is prescribed only for appropriate patients and that adverse effects (e.g., CRS and ICANS) are managed in an optimized and timely manner.	—
Pricing		
6. A reduction in price.	The ICER for tarlatamab is $559,946 per QALY gained compared with the basket comparator. A price reduction of 86% would be required for	—

Reimbursement condition	Reason	Implementation guidance
	tarlatamab to achieve an ICER of $50,000 per QALY gained compared to the basket comparator.	
Feasibility of adoption		
7. Organizational feasibility must be addressed so that jurisdictions have the infrastructure in place to implement treatment with tarlatamab including access to specialized facilities that can administer bispecific T-cell engager therapies and are equipped to manage adverse events.	Bispecific T-cell engager therapies are an emerging treatment class for solid tumours. Infrastructure to administer, monitor, and manage the known adverse events associated with these treatments (e.g., access to tocilizumab for the management of CRS, and the need to provide additional funding for inpatient therapy) are required. The limited availability of specialized treatment centres may limit access to tarlatamab.	—

CNS = central nervous system; CRS = cytokine release syndrome; ECOG = Eastern Cooperative Oncology Group; ES-SCLC = extensive-stage small cell lung cancer; ICANS = immune effector cell-associated neurotoxicity syndrome; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SCLC = small cell lung cancer.

Discussion Points

- **Unmet needs in ES-SCLC:** pERC acknowledged that ES-SCLC is a severe and debilitating disease with substantial morbidity and mortality, highlighting that there is a need for effective treatments in the third-line setting. pERC also noted the difficulty in conducting phase III randomized trials in this setting due to the limited patient population and rapid progression of the disease, and pERC agreed with the clinical experts that it is unlikely that higher-level evidence will become available in the third-line and beyond setting. pERC considered the needs identified by patients, which included prolonging life, maintaining or improving HRQoL, and reducing disease-related symptoms and treatment-related side effects. pERC noted that in the phase II, single-arm DeLLphi-301 trial, tarlatamab resulted in tumour shrinkage (ORR) in 41.4% of patients, which was significantly higher than the 15% historical benchmark used for statistical calculations, and a noteworthy duration of response (DOR) (median DOR not reached; Kaplan-Meier estimate of DOR = 64.9% at 6 months). According to the clinical experts consulted for this review, a median OS of 14.3 months and a median PFS of 4.3 months in patients in the DeLLphi-301 trial were considered clinically meaningful. However, the magnitude of benefit was unknown because of the lack of a direct comparator due to the single-arm design of the trial as well as the limitations of the ITC. pERC was unable to conclude that tarlatamab meets many of the identified significant unmet needs, such as the potential to prolong survival, improve patients' HRQoL, or reduce side effects. However, based on the input received from the clinical experts and the phase II trial results, pERC acknowledged that this drug may provide a treatment option with potentially meaningful benefit for some patients despite the uncertainties.
- **Certainty of evidence:** Although the certainty of all outcomes from the DeLLphi-301 study were considered "very low" due to the study design and potential selection bias, pERC noted that tarlatamab resulted in potentially clinically meaningful response rates indicative of drug effect with

tarlatamab. Although pERC and the clinical experts considered the results for survival in the third-line setting encouraging, pERC noted that the magnitude of the results were difficult to interpret due to the study design, a lack of comparator, and immaturity of the results at the data cut-off (DCO). pERC also discussed that no correlation between response and survival has been demonstrated in this setting.

- **Adverse effects:** pERC discussed the AE profile of tarlatamab, acknowledging the patient need for treatments with fewer side effects. pERC noted that, overall, the harms associated with tarlatamab were considered manageable according to the clinical experts. However, because of the lack of comparator in the DeLLphi-301 study and that harms were not assessed in the ITCs, pERC was unable to draw conclusions on the comparative safety of tarlatamab versus other active treatments and consequently whether tarlatamab would meet this need. pERC questioned the proportion of patients who would be eligible to receive tarlatamab given its toxicity profile and the overall health of patients in the third-line and beyond setting and they discussed the logistics of managing novel AEs in thoracic oncology, such as CRS and ICANS.
- **HRQoL:** Patients and clinicians highlighted maintenance or improvement in HRQoL as an important outcome and treatment goal in ES-SCLC. The results for HRQoL from the DeLLphi-301 trial were inconclusive due to the single-arm, open-label design and the small number of patients completing assessments at the specified time point (N = 14). As a result, pERC could not conclude that tarlatamab would meet this important need. Additionally, there were no HRQoL outcomes evaluated in the ITCs, and the comparative effect of tarlatamab on HRQoL versus other active treatments for ES-SCLC remains unknown.
- **Indirect evidence:** pERC discussed the sponsor-submitted ITCs, which included 1 propensity score weighted analysis of tarlatamab compared with available therapies for ES-SCLC in the third-line and beyond setting from the Flatiron database and 2 MAICs that compared tarlatamab with sponsor-conducted retrospective observational cohort studies based on aggregate registry data from the Cancer Analysis System (CAS) study conducted in the UK and the Oncology Outcomes Study (OOS) conducted in Canada. pERC noted that the results of the ITCs generally favoured tarlatamab over comparator therapies; however, the limitations in the analyses, including the risk of selection bias in the included studies, the heterogeneity in patient populations and study designs which resulted in a significantly reduced sample size, and the lack of adjustment for potential prognostic factors, prevented pERC from drawing conclusions on the comparative efficacy of tarlatamab patients with ES-SCLC.
- **Organizational feasibility and feasibility of adoption:** pERC discussed provision of care and system and economic considerations that were noted by the drug plans. pERC acknowledged the extensive health system resource implications pertaining to the step-up dosing and the serious warnings and precautions of administering tarlatamab. This includes administration, monitoring, and the management of AEs, particularly CRS and ICANS (patients are required to be monitored for 24 hours on cycle 1 day 1 and cycle 1 day 8, with tocilizumab readily available), for which the existing infrastructure may not be readily equipped or available at many centres in most jurisdictions. pERC and the clinical experts consulted for this review emphasized that the implementation of tarlatamab

presents unique and significant challenges for each jurisdiction because tarlatamab is 1 of the first bispecific T-cell engager therapies available for treating solid tumours and many thoracic oncologists may not have experience in managing CRS and ICANS. The sponsor's submitted economic model captured these additional costs, but these costs were not considered as part of the submitted BIA. The incremental budget impact to the Canadian health care system of reimbursing tarlatamab is likely to be higher than estimated in the CDA-AMC reanalysis because of these additional resource implications associated with the administration of tarlatamab.

- **Cost-effectiveness:** The estimated price reduction required to achieve cost-effectiveness at the threshold of $50,000 per QALY gained is highly uncertain. The ICER was heavily influenced by the modelled comparative effectiveness in which there is no direct comparative evidence to inform this set of model parameters. pERC discussed that concerns regarding the uncertainty associated with the comparative clinical efficacy lead to uncertainty associated with the incremental cost-effectiveness estimates of tarlatamab.
- **Place in therapy:** pERC discussed the Notice of Compliance with Conditions (NOC/c) issued by Health Canada for tarlatamab pending the results of the randomized, open-label, phase III DeLLphi-304 trial of tarlatamab compared with standard of care in patients with relapsed SCLC after platinum-based first-line chemotherapy. Additionally, pERC highlighted the DeLLphi-305 trial, an open-label randomized controlled trial of tarlatamab plus durvalumab compared with durvalumab alone in first-line ES-SCLC following platinum-etoposide chemotherapy with concurrent durvalumab. Both studies are expected to be completed in 2027. However, pERC noted that both studies, including the confirmatory DeLLphi-304 trial, are being conducted in a population that is different from that of this reimbursement request.

Background

Lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer-related death in Canada. SCLC is a highly aggressive and rapidly progressive lung cancer subtype, which accounts for approximately 10% to 15% of all lung cancer cases. Between 2012 to 2016 in Canada, the age-standardized incidence rate of SCLC was estimated to be 6.9 patients per 100,000 for both sexes combined and 7.3 patients per 100,000 and 6.6 patients per 100,000 for males and females, respectively. Common symptoms of SCLC include persistent cough; chest pain that gets worse when coughing, laughing, or taking a deep breath; hemoptysis; and hoarseness and/or wheezing. Some patients may also experience a loss of appetite, unintended weight loss, fatigue, and recurrent episodes of lung infections. Additionally, patient health is further compromised by toxicities during chemotherapy and side effects with current therapies. Patient's HRQoL is also significantly impaired due to anxiety, depression, and distress associated with the disease and treatments. At the time of diagnosis, approximately 70% of patients present with ES-SCLC. Their prognosis is poor, with a median OS of 12 to 13 months from the time of diagnosis and 5-year survival rates ranging from 1% to 10%.

In Canada, platinum-etoposide in combination with the programmed death-ligand 1 (PD-L1) inhibitors, either durvalumab or atezolizumab are the typical first-line treatment options for ES-SCLC. Second-line treatment options in Canada include topotecan, CAV, or rechallenge with platinum-etoposide. The prognosis for relapsed SCLC in the second-line setting is very poor. Currently, in the third-line setting, there are no Health Canada–approved treatments. Available options in this setting include rechallenging with the initial regimen and other single-agent or combination chemotherapy regimens, enrolling in clinical trials, or best supportive care.

Tarlatamab has been approved by Health Canada for the treatment of adult patients with ES-SCLC with disease progression on or after at least 2 prior lines of therapy including platinum-based chemotherapy. Tarlatamab is a bispecific delta-like ligand (DLL3)-directed CD3 T-cell engager. It is available as lyophilized powder for solution for IV infusion, 1 mg and 10 mg per vial. The recommended dose of tarlatamab is an initial dose of 1 mg on day 1, followed by 10 mg on days 8, 15, and every 2 weeks thereafter.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 ongoing, phase II, open-label, single-arm trial (DeLLphi-301) in adult patients with histologically or cytologically confirmed relapsed or refractory SCLC that progressed or recurred following 1 platinum-based regimen and at least 1 other prior line of treatment
- a review of 3 ITCs
- patients' perspectives gathered by 3 patient groups: Lung Cancer Canada (LCC), the Lung Health Foundation (LHF), and the Canadian Cancer Survivor Network (CCSN)
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with SCLC
- input from 2 clinician groups: the LCC Medical Advisory Committee and the Ontario Health Cancer Care Ontario (OH-CCO) Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

A joint patient group submission from LCC, LHF, and CCSN was received for this review. LCC is a registered national charitable organization that serves as Canada's leading resource for lung cancer education, patient support, research, and advocacy. LHF is a registered charity that assists and empowers people living with or caring for others with lung disease. CCSN is a national network of patients, families, survivors, and

community partners who take collaborative action to promote the best standards of care for cancer patients. Information provided for this submission was collected through virtual interviews with 3 patients and their caregivers between July and August 2024. Two patients were living in Canada, and 1 was in the US. All patients had ES-SCLC and had experience with tarlatamab, which was used as third-line or later therapy.

The patient groups emphasized that SCLC is an aggressive type of cancer with a high symptom burden, rapid disease progression, and poorer health outcomes. Current treatments for ES-SCLC (chemotherapy and immunotherapy) are associated with limited DOR, harsh side effects, increased dependence on caregivers in daily activities, and an impact on the patients' functionality. As such, the patient groups highlighted an urgent need for a new treatment beyond the first-line setting that should be effective in controlling the disease and symptoms, minimizing side effects of the treatments, allowing patients to maintain a meaningful quality of life, minimizing caregiver burden, delaying disease progression, and offering patients an additional treatment option upon disease progression or when other treatments are exhausted. All 3 patients who received tarlatamab indicated that this drug was effective in treating the disease and improving their quality of life compared to their previous therapies. The patients also reported significant side effects when receiving the first dose, which improved over time.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted for this review emphasized that once a patient with ES-SCLC becomes platinum-resistant, systemic therapy options become very limited with poorer response rates and reduced OS. The clinical experts indicated that the most important goals of treatment for patients with ES-SCLC are to prolong life, delay disease progression, reduce the severity of cancer-related symptoms, and improve patients' HRQoL, as well as balancing the toxicities of therapy. There are currently no Health Canada–approved treatments for ES-SCLC in the third-line or later setting. As such, the clinical experts identified the need for new safe and effective treatment options in patients with ES-SCLC with disease progression on or after at least 2 prior lines of therapy including platinum-based chemotherapy, particularly those patients with platinum-refractory disease. The clinical experts also noted there is a need for treatments in all lines of therapy that can effectively control central nervous system (CNS) metastasis because of the increased risk of CNS metastasis, which requires whole brain radiotherapy in patients with ES-SCLC.

In line with the Health Canada indication, the clinical experts indicated that tarlatamab would become the preferred treatment option for patients whose ES-SCLC progresses on or after 2 lines of therapy (i.e., third line or later). Both clinical experts noted that tarlatamab could be an option for patients with platinum-refractory disease, which would be in the second-line or later setting; however, they noted that this is not within the scope of this review and the use of tarlatamab in the second-line setting is not an approved Health Canada indication. The clinical experts also highlighted that because only a limited number of patients are likely able to receive treatment in the third-line setting due to severe functional decline or disease progression, tarlatamab is not expected to cause a major shift in the current treatment paradigm.

Per the Health Canada indication, patients with ES-SCLC with disease progression on or after at least 2 prior lines of therapy including platinum-based chemotherapy would be considered for treatment with tarlatamab. The clinical experts noted that there is currently no biomarker to determine which patients will best respond to tarlatamab and, therefore, suggested that tarlatamab should be offered to all patients who are eligible to receive this treatment. However, based on the clinical experts' experience, patients may be more likely to benefit from tarlatamab if they are younger, have fewer comorbidities or lower burden of disease, have disease that has previously responded to platinum-etoposide, or had a longer DOR to previous treatments. Meanwhile, the clinical experts acknowledged that the challenges of administering tarlatamab (e.g., hospital admission in a specialized centre is required) will limit the uptake of this treatment in practice. In addition, concerns about the AEs related to the use of tarlatamab (such as higher risk of CRS, particularly in patients with cardiac comorbidities) may also limit clinicians from administering this drug to patients who do not meet the eligibility criteria of the DeLLphi-301 trial.

The clinical experts noted that, in general, outcomes used in clinical practice align with those seen in clinical trials of ES-SCLC, which include OS, PFS, CNS metastasis-free survival, HRQoL, and symptom relief. Both clinical experts agreed that response to treatment should be assessed every 2 to 3 months with imaging examinations to determine if response or stable disease is observed. The clinical experts stated that in the third-line setting, any improvement of 2 months or greater in OS or PFS over the standard treatment options would be clinically meaningful. The experts also highlighted that there is likely variation in how clinicians would measure response or success and may also include stability or improvement of symptoms in their assessment.

The clinical experts noted that treatment with tarlatamab will be discontinued if there is evidence of disease progression, intolerable or unmanageable toxicities including grade 3 or higher CRS or ICANS, or deterioration of quality of life or if it is the patient's preference. The clinical experts also noted that if clinical benefits from treatment with tarlatamab are maintained despite evidence of radiographic progression, patients may be allowed to continue this therapy. Decisions regarding whether patients should continue treatment with tarlatamab beyond radiographic progression is at the discretion of the treating physician.

The clinical experts indicated that patients with ES-SCLC are under the care of medical oncologists and/or oncologists with experience administering and managing systemic therapy. In line with the DeLLphi-301 trial, the clinical experts noted that patients receiving treatment with tarlatamab should be hospitalized for 24 hours during cycle 1 day 1 and cycle 1 day 8 due to the increased risk of CRS and ICANS. Additionally, treatment centres must have immediate access to an onsite intensive care unit capable of managing these potentially fatal AEs. However, the clinical experts noted that, according to clinical trial guidelines, patients should initiate and receive tarlatamab in an inpatient setting; however, transition to an outpatient setting would be reasonable after 3 to 4 treatments. Furthermore, the clinical experts noted that supervision of later treatment cycles may be conducted by other practitioners in the treatment team, such as nurse practitioners or general practitioners in oncology.

Clinician Group Input

Two clinician groups provided input for the review of tarlatamab: the LCC Medical Advisory Committee and the OH-CCO Drug Advisory Committee. A total of 29 clinicians from the LCC Medical Advisory Committee and 5 clinicians from the OH-CCO Lung Cancer Drug Advisory Committee provided input for this submission.

In general, the clinician group inputs were consistent with the input provided by the clinical experts consulted for this review. The clinician groups indicated that there are limited treatment options available for patients with ES-SCLC in the second-line or later setting, and they are usually associated with suboptimal treatment effect and significant toxicities. As such, the clinician groups highlighted a pressing need for third-line or later treatment options that can prolong life, maintain quality of life, and minimize toxicities. Based on the results from clinical trials, the clinician groups suggested that tarlatamab is best suited for patients with progressive SCLC, who have exhausted 2 or more lines of therapy, who have an adequate performance status, who cannot tolerate further cytotoxic therapy, and those who can manage potential side effects from tarlatamab. The clinician groups also highlighted that tarlatamab has a unique mechanism of action (i.e., a bispecific T-cell engager agent), and speculated that tarlatamab may offer a viable treatment option for patients who have only had 1 prior treatment and are not candidates for further chemotherapy.

When assessing treatment response to tarlatamab, the clinician groups indicated that both clinical evaluations and radiologic assessments are essential, and treatment should be discontinued if there is evidence of disease progression and/or significant toxicity. Additionally, the clinician groups indicated that tarlatamab should be administered in specialized centres with an inpatient setting to handle any potential toxicities from the treatment.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
There was no comparator for tarlatamab in the phase II DeLLphi-301 trial. Generic chemotherapy (i.e., CAV or single-agent chemotherapy) would be used in patients with good performance status after 2 lines of therapy.	Comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
One of the eligibility criteria in the DeLLphi-301 trial was ECOG PS 0 to 1. Should patients with ECOG PS score ≥ 2 be considered for treatment with tarlatamab?	pERC agreed with the clinical experts who indicated that, in clinical practice, patients with an ECOG PS score of 2 may be eligible for treatment with tarlatamab. However, those with an ECOG PS score > 2 should not be treated with tarlatamab.

Implementation issues	Response
If a patient was treated with platinum-based chemotherapy in the LS-SCLC setting and then progressed to ES-SCLC and was treated with a line of treatment, does the line of therapy received in the LS-SCLC setting count as 1 of the 2 prior treatments required before tarlatamab?	pERC agreed with the clinical experts who noted that, in this particular situation, the platinum-based chemotherapy received in the LS-SCLC setting can be counted as 1 of the 2 prior treatments required before tarlatamab therapy.
Considerations for discontinuation of therapy	
As per the trial protocol for DeLLphi-301, patients with ES-SCLC were allowed to continue tarlatamab beyond radiographic progression if the investigator thought that tarlatamab provided continued clinical benefit. In this case, when should treatment with tarlatamab be discontinued?	pERC agreed with the clinical experts who indicated that if clinical benefits from treatment with tarlatamab are maintained despite evidence of radiographic progression, patients may be allowed to continue therapy in certain circumstances (e.g., no worsening of symptoms, quality of life is not declining, or the patient's overall condition remains stable). The clinical experts highlighted that, in these cases, radiation therapy can be delivered to specific metastatic lesions that are growing as determined by imaging. Decisions regarding whether patients should continue treatment with tarlatamab beyond radiographic progression is at the discretion of the treating physician. However, the experts noted that if the disease is truly progressing and the patient becomes symptomatic, the clinical benefit from tarlatamab would decline and treatment would be discontinued.
Considerations for prescribing of therapy	
Tarlatamab is administered as an IV infusion on days 1, 8 and 15 of cycle 1 and then days 1 and 15 of subsequent cycles.	Comment from the drug programs to inform pERC deliberations.
Generalizability	
Should patients currently on other systemic therapies be switched to tarlatamab?	The clinical experts indicated that in clinical practice, it is unlikely for patients with ES-SCLC to be switched to another treatment when they respond well to the current treatment. Usually in the third-line setting, the treatment effect of a drug is not durable; therefore, the physician can quickly find out whether the patient responds well to a treatment or not. If the patient has progressive disease and meets the eligibility criteria of tarlatamab, they can be offered this treatment; however, this should be considered another line of therapy, but not treatment switching.
Patients are required to be within 1 hour drive from a specialized centre (i.e., emergency department) for cycle 1 of tarlatamab in the event of the occurrence of CRS.	Comment from the drug programs to inform pERC deliberations.
Care provision issues	
A stabilizer is required for the compounding of tarlatamab to prevent adsorption of the drug to the IV bags and tubing. The product monograph includes the stabilizer within the tarlatamab package.	Comment from the drug programs to inform pERC deliberations.
CRS, ICANS, and infections can occur with tarlatamab. Monitoring of these AEs (particularly for CRS) is required, especially in cycle 1 of treatment.	Comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
Tarlatamab may require inpatient administration during the ramp up stage. Additional therapies may be required during treatment with tarlatamab to manage the adverse events (e.g., tocilizumab may be required for the management of CRS, IV steroids may be required for the management of ICANS, other drugs such as anakinra may be needed in patients who are not responding to steroids for ICANS). To ensure equitable access, the costs of these therapies, especially in the inpatient setting, need to be incorporated as part of any implementation.	Comment from the drug programs to inform pERC deliberations.
System and economic issues	
The incremental budget impact of tarlatamab to current standard of care used in Canada is substantial. The drug plans noted other system or economic issues over 3 years compared to current expenditures in the third-line setting that jurisdictions are paying for.	Comment from the drug programs to inform pERC deliberations.
Per the product monograph, patients must be monitored for 24 hours after the cycle 1 day 1 and cycle 1 day 8 doses of tarlatamab in an appropriate health care setting. Would patients be required to be treated with tarlatamab in the inpatient setting (potential additional costs to be considered include the costs of hospitalization for monitoring of CRS)? Would patients be able to start treatment with tarlatamab in an outpatient setting? If yes, which patients would be eligible to be treated in the outpatient setting, and which patients would start in inpatient setting?	The clinical experts stated that patients must be monitored for 24 hours in an inpatient setting, at least for the first 2 doses of tarlatamab (as recommended in the clinical trials). The clinical experts indicated that patients are likely to experience CRS on their first cycle of treatment and their chance of developing CRS during the second cycle is reduced. Per the product monograph, after cycle 1 day 1 and cycle 1 day 8, patients would be monitored after infusion in the outpatient setting. pERC agreed with clinical experts and noted that, to ensure patient safety, additional hospitalization may be required if CRS occurred on the previous dose of tarlatamab.
Current chemotherapy used in the third-line setting for ES-SCLC includes generic chemotherapy, although prices are confidential.	Comment from the drug programs to inform pERC deliberations.

CAV = cyclophosphamide plus doxorubicin and vincristine; CRS = cytokine release syndrome; ECOG PS = Eastern Cooperative Oncology Group performance status; ES-SCLC = extensive-stage small cell lung cancer; ICANS = immune effector cell-associated neurotoxicity syndrome; LS-SCLC = limited-stage small cell lung cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; SCLC = small cell lung cancer.

Clinical Evidence

Systematic Review

Description of Studies

One ongoing, phase II, open-label, single-arm trial, DeLLphi-301 (N = 222), was included in this review. The purpose of this study was to evaluate the efficacy and safety of tarlatamab in adult patients with histologically or cytologically confirmed relapsed or refractory SCLC that progressed or recurred following 1 platinum-based regimen and at least 1 other prior line of treatment. Patients must have had measurable lesions, as defined per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1), within 21 days before the first dose of tarlatamab and must have had adequate organ function. The study excluded

patients if they had symptomatic or untreated brain metastases. The primary efficacy end point of this study was ORR, with secondary end points of OS, PFS, exploratory end points of HRQoL, and safety. At baseline, of the 99 patients in the 10 mg group, most were men (male: 71.1%; female: 28.9%), and the median age was 64 years (range, 35 to 82 years). Overall, patients had a median of 2 (range, 1 to 6) prior lines of therapy, including 73.7% of patients with prior PD-1 or PD-L1 inhibitors. Time to progression after first-line platinum therapy was less than 90 days for 27 patients (27.3%), between 90 and 179 days for 22 patients (22.2%), longer than 180 days for 20 patients (21.4%), and unknown for 30 patients (30.3%). Most patients had metastatic disease (98.0%), no brain metastases (77.8%) or liver metastases (61.6%), and an Eastern Cooperative Oncology Group (ECOG) performance status score of 1 (73.7%).

A primary Clinical Study Report and 3 associated addenda were provided for the DeLLphi-301 trial. The primary DCO was June 27, 2023, and the most recent DCO was May 16, 2024.

Efficacy Results

Primary and secondary analyses on the efficacy outcomes were conducted in the investigator full analysis set and blinded independent central review (BICR) full analysis set.

Overall Survival

At DCO of June 27, 2023, in the tarlatamab 10 mg group (parts 1 and 2), median OS was 14.3 months (95%, 10.8 months to NE), with a median follow-up time of 10.6 months (95% CI, 9.2 to 11.5 months). The 12-month OS rate was 57.7% (95% CI, 45.0% to 68.4%).

At DCO of May 16, 2024, the median OS was 15.2 months (95% CI, 10.8 months to NE), with a median follow-up time of 20.7 months (95% CI, 19.6 to 21.7 months). The 12-month OS rate was 56.6% (95% CI, 45.6% to 66.3%).

Progression-Free Survival

At DCO of June 27, 2023, in the 10 mg group (parts 1 and 2), median PFS by BICR was 4.3 months (95% CI, 3.0 to 5.6 months) with a median follow-up time of 9.7 months (95% CI, 8.3 to 10.9 months).

At DCO of October 2, 2023, median PFS by BICR was 4.3 months (95% CI, 3.0 to 5.6 months) with a median follow-up time of 13.6 months (95% CI, 11.0 to 13.8 months).

Health-Related Quality of Life

Analyses of HRQoL end points were conducted for part 1 and part 2. As of June 27, 2023, the results for the European Organization For Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Lung Cancer Module (QLQ-LC13) (higher scores for the scales and single items representing a high level of symptomatology or problems) showed that the least squares (LS) mean changes from baseline up to cycle 12 were −4.5 (95% CI, −11.4 to 2.4) for cough, −6.5 (95% CI, −10.9 to −2.1) for chest pain, and −10.2 (95% CI, −16.4 to −4.0) for dyspnea composite score in the 10 mg group. The LS mean change from baseline up to cycle 12 for the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) subscales of global health status/quality of life (increase in this QoL scale scores reflects an improvement) was 11.5 (95% CI, 6.6 to 16.4) in the tarlatamab 10 mg group.

Objective Response Rates

As of June 27, 2023, the ORR in the BICR full analysis set for part 1 and part 2 was 41.4% (97.5% CI, 30.3% to 53.2%) for patients in the 10 mg group.

As of DCO of January 12, 2024, the ORR in the BICR full analysis set for part 1 and part 2 was 40.4% (95% CI, 30.7% to 50.7%) for patients in the 10 mg group.

The vast majority of patients achieved partial response instead of complete response in the ORR assessment.

Harms Results

Safety analyses were conducted in the safety analysis set, which included all patients who received at least 1 dose of tarlatamab.

As of DCO June 27, 2023, 99% of patients experienced treatment-emergent AEs (TEAEs) at the tarlatamab 10 mg dose. The most commonly reported all-grade TEAEs (≥ 20% of patients) in the 10 mg group were CRS (51.5%), decreased appetite (30.3%), pyrexia (39.4%), constipation (31.3%), anemia (28.3%), fatigue (23.2%), and asthenia (21.2%). Grade 3 or higher AEs were reported for 60 patients (60.6%). The most frequently reported grade 3 or higher TEAEs (≥ 5% of patients) in the 10 mg group were anemia, lymphopenia, decreased lymphocyte count, lymphopenia, hyponatremia, fatigue, and asthenia hyponatremia. Of note, CRS was the most frequently reported AE in the tarlatamab 10 mg group, but no patients in this group had grade 3 or higher CRS events.

Serious AEs (SAEs) were reported for 58 patients (58.6%) in the 10 mg dose group (part 1 and 2) and 15 patients (44.1%) in the modified safety monitoring 10 mg group as of DCO June 27, 2023. The most frequently reported (≥ 2 patients) SAEs by preferred term in the 10 mg group (part 1 and Part 2) were CRS (26.3%), pyrexia (6.1%), pneumonia (4.0%), device-related infection (3.0%), respiratory tract infection (3.0%), ICANS (2.0%), hyponatremia (4.0%). In the part 3 modified safety monitoring 10 mg target dose group, the most frequently reported (≥ 2 patients) SAEs by preferred term were CRS (14.7%) and ICANS and respiratory failure (5.9% each). The incidence of SAEs reported as of October 2, 2023, was similar to that at DCO of June 27, 2023.

AEs leading to discontinuation of tarlatamab were reported for 7 patients (7.1%) in the 10 mg group and 4 patients (11.8%) in the 10 mg modified safety monitoring group when assessed at the DCO of October 2, 2023.

Fatal AEs were reported for 2 patients (2.0%) in the 10 mg group in part 1 and part 2 and for 3 patients (8.8%) in the part 3 modified safety monitoring 10 mg group. None of the deaths were considered by the investigator to be related to tarlatamab.

In the 10 mg group (parts 1, 2, and 3), CRS occurred in 70 patients (52.6%). There was 1 patient in the 10 mg modified safety monitoring group who had a grade 3 or higher CRS event. AE data were pooled for the 10 mg group and the 10 mg modified safety monitoring group to summarize the occurrence of any grade 3 or

higher events in either group. In the 10 mg group (parts 1 and 2), 9 patients (9.1%) had ICANS events and no patients had grade 3 or higher events.

Critical Appraisal

DeLLphi-301 is an ongoing, phase II, open-label, single-arm trial evaluating the efficacy and safety tarlatamab in patients with ES-SCLC. The potential influence of selection bias is difficult to ascertain in a single-arm trial. One of the key limitations of the DeLLphi-301 trial was the absence of a comparator group. In a single-arm trial, the treatment effect of the study drug cannot be directly assessed because the trial design is not able to distinguish what proportion of the estimated treatment response can be attributed to the study drug, placebo effects, a patient's natural history, or other prognostic factors. As a single-arm trial, patients in the DeLLphi-301 trial were aware of the intervention they were taking, which potentially increased the risk of detection bias and performance bias and limited the interpretability of the subjective study outcomes, such as patient-reported outcomes including HRQoL and AEs. The primary end point of the DeLLphi-301 trial was ORR, which is directly attributable to the antitumour activity of tarlatamab despite the single-arm design. Clinically meaningful outcomes for this review included OS and PFS; however, time-to-event end points cannot be adequately assessed in a single-arm trial, so the effect of tarlatamab on these end points can only be considered as exploratory and supportive. Despite OS and PFS results that were considered clinically meaningful by the clinical experts consulted for this review, the combination of the single-arm design, the secondary nature of the outcomes, and the short follow-up duration, the results for these end points should only be considered supportive of the overall antitumour effect of tarlatamab. In this trial, patients' HRQoL was assessed using both disease-specific and generic questionnaires. However, due to the large amount of missing data, the effect of tarlatamab on patients' quality of life remains uncertain.

Based on the feedback from the clinical experts consulted for this review, the eligibility criteria and baseline characteristics of patients enrolled in the DeLLphi-301 trial generally reflected the patient population in Canadian clinical practice that would receive treatment with tarlatamab for ES-SCLC, although, in practice, this treatment may be used in a broader population than the DeLLphi-301 trial. The experts also confirmed that the use of concomitant therapies and subsequent anticancer therapies were generally consistent with Canadian practice. The outcome measures in the DeLLphi-301 trial are clinically relevant in clinical trials of ES-SCLC.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and randomized controlled trials identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Although GRADE guidance is not available for noncomparative studies, the CDA-AMC review team assessed pivotal single-arm trials for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a conclusion to be drawn

on the effect of the intervention versus any comparator, the certainty of evidence for single-arm trials started at very low certainty with no opportunity for rating up.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The target of the certainty of evidence assessment was the presence of a clinically important improvement in survival (PFS and OS) and HRQoL, which were considered the most important outcomes to treatment by the clinical experts consulted for this review, and the clinician group and patient group inputs. According to the clinical experts, clinically important thresholds for the outcomes of OS and PFS for treatment with tarlatamab were a benefit of at least 2 months over current standard of care for OS and PFS. Additionally, response to treatment (ORR) was included in the certainty of evidence assessment based on the potential translation to long-term survival outcomes.

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings from the DeLLphi-301 trial for tarlatamab for the treatment of adult patients with ES-SCLC with disease progression on or after at least 2 prior lines of therapy including platinum-based chemotherapy.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- OS
- PFS
- HRQoL measured with EORTC QLQ-C30 and EORTC QLQ-LC13
- ORR
- risk of SAEs
- risk of CRS
- risk of ICANS

Table 3: Summary of Findings for the Efficacy and Safety of Tarlatamab for Patients With ES-SCLC (No Comparator)

Outcome and follow up	Patients (studies), N	Effect	Certainty[a]	What happens
Survival				
OS (months) Median follow up (as of June 27, 2023): 10.6 months	99 (1 single-arm trial)	Median = 14.3 months (95% CI, 10.8 months to NE) 12-month rate = 57.7% (95% CI, 45.0% to 68.4%)	Very low[b]	The evidence is very uncertain about the effect of tarlatamab on OS compared with any comparator
OS (months) Median follow up (as of May 16, 2024): 20.7 months	99 (1 single-arm trial)	Median = 15.2 months (95% CI, 10.8 months to NE) 12-month rate = 56.6% (95% CI, 45.6% to 66.3%)	Very low[b]	The evidence is very uncertain about the effect of tarlatamab on OS compared with any comparator
PFS (months) Median follow up (as of June 27, 2023): 9.7 months	99 (1 single-arm trial)	Median = 4.3 months (95% CI, 3.0 to 5.6 months) 12-month rate = 25.7% (95% CI, 16.7% to 35.8%)	Very low[c]	The evidence is very uncertain about the effect of tarlatamab on PFS compared with any comparator
PFS (months) Median follow up (as of October 2, 2023): 13.6 months	99 (1 single-arm trial)	Median = 4.3 months (95% CI, 3.0 to 5.6 months) 12-month rate = 25.2% (95% CI, 16.6% to 34.7%)	Very low[c]	The evidence is very uncertain about the effect of tarlatamab on PFS compared with any comparator
HRQoL				
EORTC QLQ-C30 score, mean CFB (95% CI) Median follow up (as of June 27, 2023): 10.6 months	14 (1 single-arm trial)	**Global health status/QoL:** Mean CFB to cycle 12 = 11.50 (95% CI, 6.63 to 16.37)	Very low[c,d]	The evidence is very uncertain about the effect of tarlatamab on global health status/QoL score in EORTC QLQ-C30 compared with any comparator
EORTC QLQ-LC13 scores, mean CFB (95% CI) Median follow up (as of June 27, 2023): 10.6 months	14 (1 single-arm trial)	**Dyspnea composite score:** Mean CFB to cycle 12 = −10.21 (95% CI, −16.41 to −4.02) **Cough:** Mean CFB to cycle 12 = −4.48 (95% CI, −11.35 to 2.39) **Chest pain:** Mean CFB to cycle 12= −6.50 (95% CI, −10.94 to −2.06)	Very low[c,d]	The evidence is very uncertain about the effect of tarlatamab on dyspnea, cough, and chest pain scores in EORTC QLQ-LC13 compared with any comparator
Response to treatment				
ORR (CR + PR)(97.5% CI) Median follow up (as of June 27, 2023): NR	99 (1 single-arm trial)	N = 41 (41.4%) [97.5% CI, 30.3 to 53.2]	Very low[e]	The evidence is very uncertain about the effect of tarlatamab on ORR compared with any comparator

Outcome and follow up	Patients (studies), N	Effect	Certainty[a]	What happens
ORR (CR + PR) (95% CI) Median follow up (as of January 12, 2024): NR	99 (1 single-arm trial)	N = 40 (40.4%) [95% CI, 30.7 to 50.7]	Very low[e]	The evidence is very uncertain about the effect of tarlatamab on ORR compared with any comparator
Harms				
Patients with ≥ 1 SAE Median follow up (as of October 2, 2023): NR	99 (1 single-arm trial)	586 per 1,000 patients	Very low[f]	The evidence is very uncertain about the effect of tarlatamab on the risk of SAE compared with any comparator
Patients with CRS Median follow up (as of October 2, 2023): NR	99 (1 single-arm trial)	515 per 1,000 patients	Very low[f]	The evidence is very uncertain about the effect of tarlatamab on the risk of CRS compared with any comparator
Patients with ICANS Median follow up (as of October 2, 2023): NR	99 (1 single-arm trial)	91 per 1,000 patients	Very low[g]	The evidence is very uncertain about the effect of tarlatamab on the risk of ICANS compared with any comparator

CFB = change from baseline; CI = confidence interval; CR = complete response; CRS = cytokine release syndrome; ES-SCLC = extensive-stage small cell lung cancer; HRQoL = health-related quality of life; ICANS = immune effector cell-associated neurotoxicity syndrome; NE = not estimable; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1.

Notes: PFS and ORR were assessed with RECIST 1.1 by blinded independent central review.

All serious concerns with study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias are documented in the table footnotes.

[a]In absence of a comparator arm, conclusions about efficacy relative to any comparator cannot be drawn and certainty of evidence started at very low.

[b]In the DeLLphi-301 trial, statistical testing for this outcome was not adjusted for multiplicity. However, despite the study limitations resulting in the certainty of evidence starting as "very low," the effect size of improvement in OS (median OS = 14 to 15 months) was considered large in the third-line setting by the clinical experts consulted for this review.

[c]In the DeLLphi-301 trial, statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

[d]Rated down 2 levels for very serious study limitations due to the very low completion rate for HRQoL questionnaires (data were available for only 14% of the study population at cycle 12). Rated down 1 level because statistical testing for this outcome was not adjusted for multiplicity in the DeLLphi-301 trial and should be considered as supportive evidence.

[e]Despite the study limitations resulting in the certainty of evidence starting as "very low," the effect size of change in response rate was considered large (compared to OR of approximately15% for conventional treatments) by the clinical experts consulted for this review. In the DeLLphi-301 trial, this was a primary efficacy outcome. However, the outcome could be rated down 1 level for serious indirectness as a surrogate outcome of OR was used as the primary outcome in the place of OS and PFS, and the clinical experts consulted for this review noted that ORR is not a clinically meaningful outcome in clinical trials of SCLC, unless it is interpreted with other efficacy outcomes.

[f]Despite the relatively high incidence rate for SAEs and CRS (in more than 50% of patients), conclusions about the effect of tarlatamab relative to any comparator cannot be drawn in absence of a comparator arm, and certainty of evidence started at very low.

[g]Rated down 1 level for serious imprecision due to the low event rate in a small patient population.

Source: Primary Clinical Study Report for DeLLphi-301, Addendum 01 to the Primary Clinical Study Report for DeLLphi-301, Addendum 02 to the Primary Clinical Study Report for DeLLphi-301, and Addendum 03 to the Primary Clinical Study Report for DeLLphi-301. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

No relevant long-term extension studies were submitted by the sponsor for this review.

Indirect Comparisons

Description of Studies

In the absence of head-to-head evidence comparing tarlatamab to other relevant therapies used to manage ES-SCLC, the sponsor submitted 1 analysis using propensity score weighting (DeLLphi-301 versus Flatiron) and 2 MAICs (DeLLphi-301 versus CAS and DeLLphi-301 versus OOS) that indirectly compared OS and PFS of tarlatamab with currently available treatments in patients with ES-SCLC in the third-line and beyond setting. The DeLLphi-301 trial versus Flatiron analysis assessed additional outcomes of interest, including ORR and time to treatment discontinuation (TTD) or death. The comparator studies (Flatiron, CAS, and OOS) were conducted based on registry data collected by the sponsor.

Efficacy Results

In the DeLLphi-301 versus Flatiron study analysis, 97 patients were included in the tarlatamab cohort. The effective sample size for the comparator therapies cohort was 62 (53.4% of the original sample size) after weighting. The effective sample size for the tarlatamab cohort after match adjustment was 27.05 (27.9% of the original sample size) for the DeLLphi-301 versus CAS study analysis and 59.65 (61.5% of the original sample size) for the DeLLphi-301 versus OOS analysis. The comparator therapies cohort in the DeLLphi-301 versus CAS analysis and the DeLLphi-301 versus OOS analysis consisted of 540 and 71 patients, respectively.

Overall Survival

In the DeLLphi-301 versus Flatiron study analysis, median OS was 14.3 months (95% CI, 10.5 months to NE) for the tarlatamab cohort versus 6.6 months (95% CI, 4.8 to 10.2 months) for the comparator therapies cohort after weighting. The hazard ratio (HR) for OS (with postprogression adjustment) between the tarlatamab cohort and the weighted comparator therapies cohort was [redacted] (95% CI, [redacted] to [redacted]; P = 0.003), in favour of tarlatamab. These results were consistent with the OS analysis that did not adjust for postprogression use of tarlatamab. Results of the sensitivity analyses were consistent with the primary analysis.

Following match adjustment, the HR of OS in the base case favoured tarlatamab over comparator therapies for the DeLLphi-301 versus CAS study MAIC (HR = [redacted]; 95% CI, [redacted] to [redacted]; P = 0.0001) and the DeLLphi-301 versus OOS MAIC (HR = 0.291; 95% CI, 0.184 to 0.459; P = 0.0000). Results of the scenario analyses were consistent with the base-case analysis.

Progression-Free Survival

In the DeLLphi-301 versus Flatiron study analysis, median PFS was 4.9 months (95% CI, 2.9 to 6.7 months) for the tarlatamab cohort versus 3.0 months (95% CI, 1.9 to 3.9 months) for the comparator therapies cohort after weighting, with an HR of [redacted] (95% CI, [redacted] to [redacted]; P = 0.021) in favour of tarlatamab. Results of the sensitivity analyses were consistent with the primary analysis.

Following match adjustment, the HR of PFS in the base case favoured tarlatamab over comparator therapies for the DeLLphi-301 versus CAS study MAIC (HR = 0.184; 95% CI, 0.100 to 0.338; P = 0.0000) and the DeLLphi-301 versus OOS MAIC (HR = 0.326; 95% CI, 0.215 to 0.493; P = 0.0000). Results of the scenario analyses were consistent with the base-case analysis.

Objective Response Rate

In the DeLLphi-301 versus Flatiron study analysis, the ORR was 40% for the tarlatamab cohort versus 23% for the comparator therapies cohort after weighting, with an odds ratio of 2.29 (95% CI, 1.05 to 5.58; P = 0.05), which was in favour of tarlatamab. Results of the sensitivity analyses were, in general, consistent with the primary analysis, except for the sensitivity analysis in which prognostic factors of low importance were adjusted for in addition to factors of high and medium importance, and results did not favour either intervention.

This outcome was not assessed in the DeLLphi-301 versus CAS and the DeLLphi-301 versus OOS analyses.

Time to Treatment Discontinuation or Death

In the DeLLphi-301 versus Flatiron study analysis, the median time to TTD or death was 3.65 months (95% CI, 2.37 to 5.36 months) for the tarlatamab cohort versus 2.33 months (95% CI, 1.41 to 3.25 months) for the comparator therapies cohort after weighting. The HR of TTD or death (with postprogression adjustment) between the tarlatamab cohort and the weighted comparator therapies cohort was [redacted] (95% CI, [redacted] to [redacted]; P = 0.010), in favour of tarlatamab. Results were consistent with the TTD or death analysis that was not adjusted for postprogression use of tarlatamab.

This outcome was not assessed in the DeLLphi-301 versus CAS and the DeLLphi-301 versus OOS analyses.

Harms Results

Harms outcomes were not assessed in the studies.

Critical Appraisal

There is a risk of selection bias because the comparator studies (Flatiron, CAS, and OOS studies) selected for inclusion in the analysis were identified in the absence of prespecified methods. Other limitations included the heterogeneity between included studies regarding patient population, specifically with respect to life expectancy at baseline (in all 3 analyses); definitions of PFS; and temporal discordance in data collection period (during which a major change in treatment pattern occurred), as well as inability to adjust for potential prognostic factors (e.g., number of prior lines of therapy, previous use of PD-1 or PD-L1 inhibitor). In addition, there remained to be imbalance in several baseline patient characteristics that were identified as potential prognostic factors following weighting in the DeLLphi-301 versus Flatiron analysis. These limitations likely introduce bias due to confounding in the relative treatment effect estimates. A sizable reduction in effective sample size after the weighting process was observed in all studies, suggesting that there was a poor population overlap between studies and that the results may be heavily influenced by a subset of the sample in the trials who may not be representative of the full sample. HRQoL and harms outcomes, which

are important to patients and clinicians, were not assessed in the analyses, which represents a gap in the evidence.

Studies Addressing Gaps in the Evidence From the Systematic Review

No relevant studies addressing gaps in the evidence from the systematic review were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with ES-SCLC after platinum-based chemotherapy and at least 1 other treatment
Treatment	Tarlatamab
Dose regimen	IV infusion with a step-up dose of 1 mg on day 1, followed by a 10 mg dose on days 8 and 15, and every 2 weeks thereafter in a 28-day cycle until disease progression
Submitted price	$1,545.00 per 1-mg vial $15,450.00 per 10-mg vial
Submitted treatment cost	$27,740 for first 28-day cycle and $26,420 for subsequent cycles
Comparator	Basket comparator consisting of topotecan, combination therapy of a platinum agent and etoposide, combination therapy of CAV, etoposide, and irinotecan
Perspective	Canadian publicly funded health care payer
Outcomes	Life-years, QALYs
Time horizon	Lifetime (20 years)
Key data sources	DeLLphi-301: A phase II, open-label, single-arm, multinational trial for tarlatamab Comparative efficacy of tarlatamab with basket comparator informed by sponsor's submitted patient-level ITC based on the Flatiron external control cohort
Key limitations	• The comparative efficacy and safety of tarlatamab relative to the basket comparator for adult patients with ES-SCLC in the third-line setting is uncertain owing to the lack of direct head-to-head trials and the limitations with the sponsor's submitted ITC. Key limitations with the indirect evidence include a risk of selection bias, the sizable reduction in effective sample size, heterogeneity in patient population and study design, and an inadequate or lack of adjustment for potential prognostic factors that may introduce unmeasurable confounding in the relative treatment effect estimates. This introduces substantial uncertainty to the magnitude of clinical benefit of tarlatamab relative to the basket comparator. According to clinical expert feedback obtained by CDA-AMC, the sponsor's selected OS and PFS curves likely overestimated long-term survival outcomes. • The sponsor's use of a reduced RDI for tarlatamab, based on the DeLLphi-301 trial does not account

Component	Description
	for other factors affecting dose adjustments, such as dose delays and stepped-up therapy. Given most regimens within the basket comparator had a higher RDI assumed, the sponsor's RDI selection for tarlatamab would likely be biased in favour of tarlatamab. • The health utilities for progression-free (0.834) and postprogression (0.755) health states lacked face validity because the quality of life of those in the progression-free state was comparable to the quality of life of an age-matched Canadian general population (0.839). A published literature review indicated lower utilities for both health states within this patient population.
CDA-AMC reanalysis results	• For the CDA-AMC base case, alternative parametric functions to extrapolate OS and PFS for both tarlatamab and the basket comparator were selected, 100% RDI for all treatments was assumed, and alternative health utilities were selected for the progression-free and postprogression health states. • In the CDA-AMC base case, tarlatamab is associated with an ICER of $559,946 per QALY gained (incremental costs = $222,201; incremental QALYs = 0.40). A price reduction of 86% for tarlatamab (from $1,545 to $222 per 1-mg vial and $15,450 to $2,220 per 10-mg vial) would be necessary to achieve cost-effectiveness at $50,000 per QALY gained.

CAV = cyclophosphamide, doxorubicin, and vincristine; CDA-AMC = Canada's Drug Agency; ES-SCLC = extensive-stage small cell lung cancer; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; RDI = relative dose intensity.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the rate of uptake of tarlatamab is uncertain, duration of treatment did not align with the duration of treatment predicted in the sponsor's economic evaluation, wastage was not assumed, and the introduction of tarlatamab may have broader health care system impacts that are not addressed within the submitted BIA. The CDA-AMC reanalysis aligned the duration on treatment to reflect the duration predicted within the submitted economic model and assumed wastage on the comparator treatments. In the CDA-AMC base case, the 3-year budget impact of reimbursing tarlatamab is expected to be $33,259,139 (year 1 = $8,530,040; year 2 = $10,270,385; year 3 = $14,270,385). A health care perspective was not considered within the BIA. Tarlatamab also requires the first 2 doses be administered in a hospital inpatient setting and may require additional days of hospitalization for patients with CRS and ICANS AEs. These additional costs were not considered within the BIA.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: January 8, 2025

Regrets: One expert committee member did not attend.

Conflicts of interest: One expert committee member did not participate due to considerations of conflict of interest.

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

ISSN: 2563-6596

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.