CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761344Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761344
PDUFA Goal Date	June 12, 2024
TTT #	2023-6461
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	May 15, 2024
Subject	Evaluation of Need for a REMS
Established Name	tarlatamab-dlle
Trade Name	Imdelltra
Name of Applicant	Amgen Inc.
Therapeutic Class	delta-like ligand 3 (DLL3)-directed T-cell engager
Formulation(s)	1 mg and 10 mg lyophilized powder for injection
Dosing Regimen	1 mg followed by 10 mg on Day 8, 15, and every 2 weeks thereafter administered intravenously

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, Imdelltra (tarlatamab-dlle), is necessary to ensure the benefits outweigh its risks. Tarlatamab-dlle will herein be referred to as tarlatamab. Amgen Inc. submitted a Biologics License Application (BLA) 761344 for tarlatamab with the proposed indication: for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. The Applicant did not submit a REMS or risk management plan with this application.

Results from Part 1 and 2 of Study 20200491 (DeLLphi-301; n = 99) showed an overall response rate (ORR) of 40% (95% CI: 31, 51) and a median duration of response (DoR) of 9.7 months. DRM and the Division of Oncology 2 (DO2) agree that a REMS is not needed to ensure the benefits of tarlatamab outweigh its risks.

The key safety concerns for tarlatamab are cytokine release syndrome (CRS) and neurologic toxicity include immune effector cell-associated neurotoxicity syndrome (ICANS). Other safety concerns include hepatoxicity, infections, cytopenias, and hypersensitivity. CRS and neurologic toxicity, including ICANS are addressed in the Warnings and Precautions section of the label and with a Boxed Warning. The Applicant did not provide study investigators with any specific education and training for managing CRS and neurotoxicity including ICANS outside of the standard clinical protocol training. The rates of CRS and neurotoxicity including ICANS are of low grade and similar to other BiTEs approved without a REMS.

If approved, tarlatamab will likely be administered in the inpatient and outpatient setting by oncologists. It will be the first bispecific T-cell engager (BiTE) targeting a solid tumor. While some prescribers may be familiar with the risks of CRS and neurologic toxicity including ICANS, there may be prescribers with limited or no experience managing these risks, primarily oncologists in the outpatient/community setting. However, because tarlatamab will be administered as an intravenous infusion and the patient should be monitored for 22-24 hours on Cycle 1 (Day 1 and Day 8) in an appropriate healthcare setting, it is expected that the prescribing oncologist will monitor patients for the risks associated with tarlatamab. Because of the recommendations for monitoring, both inpatient and hospital-based outpatient infusion centers would be considered appropriate healthcare settings for tarlatamab administration.

The review team determined, if approved, the risks of tarlatamab will be conveyed through labeling. If approved, enhanced pharmacovigilance will help inform safety issues post-marketing. Additionally, a post-marketing requirement (PMR) will be issued to conduct an integrated safety analysis of data from patients with extensive stage small cell lung cancer to further characterize the long-term incidence, severity, and outcome of the known serious risks of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and neurologic toxicity.

Based on the study results and limited treatment options in this patient population constituting an unmet medical need, the FDA review team recommends accelerated approval for tarlatamab for the following indication: treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, Imdelltra (tarlatamab-dlle), is necessary to ensure the benefits outweigh its risks. Tarlatamab-dlle will herein be referred to as tarlatamab. Amgen Inc. submitted a Biologics License Application (BLA) 761344 for tarlatamab with the proposed indication: for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.[1] This application is under review in the Division of Oncology 2 (DO2).

The Applicant did not submit a REMS with this application.

2 Background

2.1 Product Information

Imdelltra (tarlatamab-dlle), a new molecular entity,[a] is a bispecific T-cell engager (BiTE) that binds to delta-like ligand 3 (DLL3) expressed on the surface of T-cells causing T-cell activation, production of inflammatory cytokines, and release of cytolytic proteins resulting in redirected lysis of DLL3-expressing cells. Tarlatamab is proposed for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. Tarlatamab is a sterile, preservative-free white to slightly yellow, lyophilized powder supplied as 1 mg and 10 mg single dose vial, for injection only.[1]

The FDA-approved indication will be:[2] for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

Tarlatamab is administered as an intravenous (IV) infusion over one hour. It is administered following a step-up dose to reduce the incidence and severity of CRS. After the step-up dose, tarlatamab is administered biweekly (every 2 weeks) until disease progression or unacceptable toxicity.[2,b]

Table 1:[2] Recommended Dosage and Schedule of Imdelltra (tarlatamab)

Dosing Schedule	Day	Dose of IMDELLTRA	Administration Instructions	Required Monitoring
Step-up Dosing Schedule Cycle 1	Day 1[1]	Step-up dose[1] 1 mg	Administer IMDELLTRA as a 1-hour intravenous infusion in an appropriate	Monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting. Recommend that patients remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA, accompanied by a caregiver.
	Day 8[1]	10 mg[1]		

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

	Day 15	10 mg	healthcare setting.	Observe patients for 6-8 hours post IMDELLTRA infusion.[2]
Cycle 2	Day 1 and 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion.[2]
Cycles 3 and 4	Day 1 and 15	10 mg		Observe patients for 3-4 hours post IMDELLTRA infusion.[2]
Cycle 5 and subsequent infusions	Day 1 and 15	10 mg		Observe patients for 2 hours post IMDELLTRA infusion.[2]

[1]Administer recommended concomitant medications before and after Cycle 1 IMDELLTRA infusions as described in Table 3 of the label.
[2]Extended monitoring in a healthcare setting is not required unless the patient experiences Grade ≥ 2 CRS, ICANS or neurological toxicity during prior treatments. See Tables 5 and 6, in the label, for monitoring recommendations.

Tarlatamab is not approved in any other jurisdiction.

2.2 BISPECIFIC T-CELL ENGAGERS (BITES)

BiTEs are antibodies that simultaneously target two different antigens for cancer treatment via redirecting immune cells to tumor cells, delivering drugs to tumors, and blocking two biological pathways significant for tumors.[3] These bispecific antibodies are associated with the risks of CRS and neurologic toxicity including ICANS. The following table shows the FDA-approved BiTEs and their respective risk mitigation.

Table 2:[4] FDA-Approved Bispecific T-Cell Engagers

BiTEs	Route of Administration	Risk Mitigation
Columvi (glofitimab-gxbm)	Intravenous	Boxed Warning: CRS Warnings and Precautions: Neurologic toxicity including ICANS
Epkinly (epcoritamab-bysp)	Subcutaneous	Boxed Warning: CRS and ICANS
Lunsumio (mosunatuzumab-axgb)	Intravenous	Boxed Warning: CRS Warnings and Precautions: Neurologic toxicity including ICANS
Kimmtrak (tebentafusp-tebn)	Intravenous	Boxed Warning: CRS
Tecvayli (teclistamab-cqyv) and	Subcutaneous	REMS with Elements to Assure Safe Use (ETASU): Tecvayli and Talvey REMS: • Prescriber certification • Pharmacy and Healthcare setting certification Boxed Warning: CRS and Neurologic toxicity including ICANS
Talvey (talquetamab-tgvs)	Subcutaneous	
Elrexfio (elranatamab-bcmm)	Subcutaneous	REMS with ETASU: Elrexfio REMS • Prescriber certification • Pharmacy and Healthcare setting certification Boxed Warning: CRS and Neurologic toxicity including ICANS
Blincyto (blinatumomab)	Intravenous	Communication Plan REMS eliminated on 12/2022 Boxed Warning: CRS and Neurologic toxicity

2.3 REGULATORY HISTORY

- **07/18/2017**: IND 134859 submitted for Study 20160323, the first-in-human study of tarlatamab subjects with SCLC.
- **12/27/2018**: Orphan Drug Designation was granted to tarlatamab for the treatment of SCLC.
- **10/12/2023**: BLA 761344 was submitted for tarlatamab for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.
- **04/15/2024:** A Post Late-Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that after carefully considering the need for a Risk Evaluation and Mitigation Strategy (REMS), given the major identified safety finding of CRS and neurologic toxicity, including ICANS, it was determined a REMS is not needed.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Lung cancer is the leading cause of death in the United States (U.S.). It accounts for 1 in 5 of all cancer deaths. In 2024, the American Cancer Society estimates approximately 234,580 new cases of lung cancer and 125,070 deaths due to lung cancer in the U.S.[5] Small cell lung cancer (SCLC) represents about 15% of all lung cancers.[c] It is a neuroendocrine tumor that is differentiated from other lung cancers by its rapid doubling time, high growth fraction, and the early development of metastases.[6] The 5-year relative survival rate for patients with localized (30%), regional (18%), and distant (3%) SCLC disease varies markedly, depending on the stage at diagnosis.[5]

SCLC is often categorized as either limited stage or extensive stage. Limited stage means that the cancer is only on one side of the chest and can be treated with a single radiation field. Extensive stage is cancer that has spread widely throughout the lung, to the other lung, or to other parts of the body (including the bone marrow).[5] Extensive state SCLC (ES-SCLC) is a serious and life-threatening condition with poor survival.[7,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

For ES-SCLC, surgery and radiation therapy are not useful as the ES-SCLC has spread too far. The standard of care for initial treatment of ES-SCLC includes platinum-based chemotherapy in combination with etoposide plus an immune checkpoint inhibitor. Platinum chemotherapy options include carboplatin and cisplatin. The two immune checkpoint inhibitors FDA-approved as 1st line to treat ES-SCLC are atezolizumab and durvalumab.[8,9] Cisplatin and etoposide plus atezolizumab is an example of an initial regimen to treat ES-SCLC.[6]

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*
[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

For the patient population pertinent to this review (ES-SCLC with disease progression on or after platinum-based chemotherapy), there are limited treatment options. Only two drugs are FDA-approved for this population, topotecan and lurbinectedin. Topotecan is indicated to treat SCLC (as a single agent) in patients with platinum-sensitive disease that has progressed at least 60 days after initiation of first-line chemotherapy.[10] Lurbinectedin is indicated to treat metastatic SCLC in adults with disease progression on or after platinum-based chemotherapy.[11] Based on the limited number of approved treatment options, this indicates there is an unmet medical need for patients with ES-SCLC with progression after prior platinum-containing therapy, particularly in patients with platinum-resistant disease.[7]

4 Benefit Assessment

The efficacy and safety of tarlatamab was evaluated in Study 20200491 (DeLLphi-301; NCT 05060016), an ongoing, Phase 2, open-label, multicenter trial in patients with relapsed/refractory SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy. The enrolled patients were required to have an ECOG Performance Status of 0 or 1 and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

Study 20200491 was conducted in three parts:

1. Part 1: evaluate safety and efficacy of two dose levels of tarlatamab (10 mg and 100 mg)
2. Parts 1 and 2: evaluate antitumor activity of tarlatamab as determined by ORR
3. Part 3: evaluate safety of reduced mandatory monitoring period in Cycle 1 at selected dose of tarlatamab

The primary efficacy population consisted of 99 patients enrolled in Part 1 and Part 2 of the study who received the proposed dosing regimen (initial dose of 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter until disease progression or unacceptable toxicity). The major efficacy outcome measures were overall response rate (ORR) and duration of response (DoR), as evaluated by Blinded Independent Committee Review (BICR) according to RECIST v1.1.[e] Results showed an ORR of 40% (95% CI: 31, 51) and a median DoR of 9.7 months (95% CI: 2.4, 20.7+). FDA considers the response rate, supported by DoR as an approvable endpoint for SCLC because in the absence of therapy, tumors grown or remain stable rather than shrink. The observed response rates from patients enrolled or randomized to Parts 1 and 2 in Study 20200491 who received tarlatamab at the proposed dosing regimen were clinically meaningful and were seen across most patient subgroups including across DLL3 expression cut-offs.[7]

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

5 Risk Assessment & Safe-Use Conditions

The safety of tarlatamab was evaluated in Study 20160323 (DeLLphi-300; NCT 03319940) and Study 20200491 (discussed in Section 4). Study 20160323 was an open-label, multi-dose, Phase 1 study evaluating the safety, tolerability, and pharmacokinetics in patients with SCLC (first-in-human).

In these two studies, patients with ES-SCLC who were exposed to intravenous tarlatamab, as a single agent, at the recommended dosage of 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8 and 15, and then every 2 weeks until disease progression or intolerable toxicity comprise the pooled safety population (N = 187). The data from the pooled safety population informs both the Adverse Reactions and Warning and Precautions section of the proposed tarlatamab label.

The most common adverse reactions (> 20%) in patients receiving tarlatamab were cytokine release syndrome (55%), fatigue (51%), pyrexia (36%) dysgeusia (36%), decreased appetite (34%), musculoskeletal pain (30%), constipation (30%), anemia (27%), and nausea (22%).[f] Serious adverse reactions occurred in 58% of patients who received tarlatamab. Serious adverse reactions in > 3% of patients included cytokine release syndrome (24%), pneumonia (6%), pyrexia (3.7%) and hyponatremia (3.6%).[g] Fatal adverse reactions occurred in 2.7% of patients who received tarlatamab (within 30 days of the last dose) including pneumonia (0.5%), aspiration (0.5 %), pulmonary embolism (0.5%), respiratory acidosis (0.5%), and respiratory failure (0.5%). The FDA assessed the Applicant's attribution of deaths and determined there were no inconsistencies.[7]

The review team determined the key safety concerns for tarlatamab are CRS and neurologic toxicity, including ICANS. Other safety concerns include hepatotoxicity, infections, cytopenias, and hypersensitivity. If approved, the risks of tarlatamab will be conveyed through labeling and enhanced pharmacovigilance will help inform of safety issues post-marketing.[7] Additionally, a post-marketing requirement (PMR) will be issued to conduct an integrated safety analysis of data from patients with extensive stage small cell lung cancer to further characterize the long-term incidence, severity, and outcome of the known serious risks of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and neurologic toxicity. This postmarketing requirement is intended to provide additional safety information that is needed to support the safety of the product.[7]

5.1 Cytokine Release Syndrome

Based on tarlatamab's mechanism of action, CRS, is an expected adverse reaction. In the pooled safety population, CRS occurred in 55% of patients, including 34% Grade 1, 19% Grade 2, 1.6% Grade 3 and 0.5% Grade 4. Recurrent CRS occurred in 24% of tarlatamab-treated patients with 18% of patients

[f] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

experiencing Grade 1 recurrence and 6% of patients experiencing Grade 2 recurrence. No grade 5 events of CRS occurred. Most events (43%) of CRS occurred after the first dose with 29% of patients experiencing any grade CRS after the second dose and 9% of patients experiencing CRS following the third dose or later. Following the Day 1, Day 8, Day 15 infusions, 16%, 4.3%, and 2.1% of patients experienced ≥ Grade 2 CRS, respectively. The median time to onset of all grade CRS from the most recent dose of tarlatamab was 13.5 hours (range: 1 to 268 hours).

The serious risk of CRS, which may be life-threatening, will be communicated in labeling with a Boxed Warning and in the Warnings and Precautions section.

For CRS, the label includes the signs and symptoms of CRS and advises healthcare providers to follow the recommended step-up dosing and to administer concomitant medications before and after Cycle 1 to reduce the risk of CRS. Patients should be well hydrated. Also, tarlatamab should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as CRS and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS).[7]

The label also advises:[7]

- Due to the risk of CRS and neurologic toxicity, including ICANS, monitor patients from the start of the tarlatamab infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting.
- At the first sign of CRS, immediately discontinue tarlatamab infusion, evaluate the patient for hospitalization and institute supportive care based on severity.
- Withhold or permanently discontinue tarlatamab based on severity.

Counsel patients to seek medical attention should signs or symptoms of CRS occur.

5.2 NEUROLOGIC TOXICITY INCLUDING ICANS

Tarlatamab can cause severe or life-threatening neurologic toxicity including ICANS. In the pooled safety population, neurologic toxicity including ICANS, occurred in 47% of patients who received tarlatamab, including 6% Grade 3. The most frequent neurologic toxicities were headache (14%), peripheral neuropathy (7%), dizziness (7%) insomnia (5%), muscular weakness (3.7%), delirium (2.1%), syncope

(1.1%), and neurotoxicity (1.1%). ICANS occurred in 9% of tarlatamab-treated patients. Recurrent ICANS occurred in 1.6% of patients. Most patients experienced ICANS following cycle 2 day 1 (24%). The median time to onset of ICANS from the first dose of tarlatamab was 29.5 days (range: 1 to 154 days), however, ICANS can occur several weeks following administration of tarlatamab.

The Warnings and Precautions section of the proposed tarlatamab label states to advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, in the event of any neurologic symptoms until they resolve. The label also advises to closely monitor patients for signs and symptoms of neurologic toxicity and ICANS during treatment. At the first sign of ICANS, the healthcare provider should immediately evaluate the patient and provide supportive therapy based on severity. Tarlatamab should be withheld or permanently discontinued based on severity.

5.3 CYTOPENIAS

Tarlatamab can cause cytopenias including neutropenia, thrombocytopenia, and anemia. In the pooled safety population, decreased neutrophils occurred in 12% including 6% Grade 3 or 4 of tarlatamab-treated patients with the median time to onset for Grade 3 or 4 being 29.5 days (range: 2 to 213). Decreased platelets occurred in 33% including 3.2% Grade 3 or 4 with the median time to onset for Grade 3 or 4 being 50 days (range: 3 to 420). Decreased hemoglobin occurred in 58% including 5% Grade 3 or 4. Febrile neutropenia occurred in 0.5% of patients treated with tarlatamab.

The proposed tarlatamab label advises healthcare providers to monitor patients for signs and symptoms of cytopenias and perform complete blood counts prior to treatment with tarlatamab, and then as clinically indicated. The label also advises to temporarily withhold or permanently discontinue tarlatamab based on the severity of the cytopenias.

5.4 INFECTIONS

Tarlatamab can cause serious, including life-threating and fatal, infections. Infections including opportunistic infections occurred in 39% of patients who received tarlatamab. Grade 3 or 4 infections occurred in 11%, and serious infections occurred in 12% of patients. The most frequent infections were COVID-19 (9%, majority during the COVID-19 pandemic), urinary tract infection (10%), pneumonia (9%), respiratory tract infection(3.2%), and candida infection (3.2%). The proposed tarlatamab label advises to monitor patients for signs and symptoms of infection prior to and during treatment with tarlatamab and treat as clinically indicated. Tarlatamab should be withheld or permanently discontinued based on severity.

5.5 HEPATOXICITY

Tarlatamab can cause hepatoxicity with elevated liver enzymes. Elevated ALT occurred in 42% with Grade 3 or 4 ALT elevation occurring in 2.1% of tarlatamab-treated patients. Elevated AST occurred in 4.4% of patients, with Grade 3 or 4 AST elevation occurring in 3.2%. Elevated bilirubin occurred in 15% of patients, with Grade 3 or 4 total bilirubin elevations occurred in 1.6% of patients. The tarlatamab proposed label advisees to monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Tarlatamab should be withheld or permanently discontinued based on severity.

5.6 EMBRYO-FETAL TOXICITY

Based on its mechanism of action, tarlatamab may cause fetal harm when administered to a pregnant woman. The Warnings and Precautions section of the proposed label states to advise patients of the potential risk to a fetus and females of reproductive potential to use effective contraception during treatment with tarlatamab and for 2 months after the last dose.

6 Expected Postmarket Use

If approved, tarlatamab will likely be administered in the inpatient and outpatient setting by oncologists. It will be the first BiTE targeting a solid tumor. While some prescribers may be familiar with the risks of CRS and neurologic toxicity including ICANS, there may be prescribers with limited or no experience managing these risks, primarily oncologists in the outpatient/community setting. However, because tarlatamab will be administered as an intravenous infusion and the patient should be monitored for 22-24 hours on Cycle 1 (Day 1 and Day 8) in an appropriate healthcare setting, it is expected that the prescribing oncologist will monitor patients for the risks of CRS and neurotoxicity including ICANS, that are associated with tarlatamab. Because of the recommendations for monitoring, both inpatient and hospital-based outpatient infusion centers would be considered appropriate healthcare settings for tarlatamab administration.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for tarlatamab beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

Based on the efficacy results and limited available therapy in this patient population constituting an unmet medical need, the FDA review team recommends accelerated approval for tarlatamab for the following indication: treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.[7] Under the FDA Accelerated Approval Program, the Applicant is required to conduct studies to confirm the anticipated clinical benefit.[12] Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial, conducted as a post-marketing requirement (PMR).[7]

Lung cancer is the leading cause of death in the U.S. and accounts for 20% of all cancer deaths. In 2024, the American Cancer Society estimates approximately 234,580 new cases of lung cancer and 125,070 deaths due to lung cancer in the U.S., 15% of these cases being SCLC. The 5-year relative survival rate for patients with SCLC is dependent on whether it is localized (30%), regional (18%), or distant (3%). If approved, tarlatamab will be the first and only FDA-approved therapy for platinum-resistant ES-SCLC.

The key safety concerns for tarlatamab are cytokine release syndrome (CRS) and neurologic toxicity include immune effector cell-associated neurotoxicity syndrome (ICANS). CRS and neurologic toxicity, including ICANS are addressed in the Warnings and Precautions section of the label and with a Boxed Warning. Labeling specifies that tarlatamab should only be administered by a qualified healthcare

professional with appropriate medical support to manage severe reactions such as CRS and neurologic toxicity including (similar to other approved BiTEs). Labeling also specifies that patients should be monitored from the start of the tarlatamab infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting. The monitoring recommendations mirror the clinical trial protocol and guidelines for grading and management of CRS and ICANS are in the label, which is also similar to other BiTEs.

Importantly, the Applicant did not provide study investigators with any specific education and training for managing CRS and neurotoxicity including ICANS outside of the standard clinical protocol training. The rates of CRS and neurotoxicity including ICANS are of low grade and similar to other BiTEs approved without a REMS. While some oncologists may be familiar with the risks of CRS and neurologic toxicity including ICANS, there may be those with limited or no experience managing these risks, primarily oncologists in the outpatient/community setting. However, due to the administration and monitoring recommendations for tarlatamab, it is expected that the prescribing oncologist will monitor patients for the risks associated with tarlatamab.

The chimeric antigen receptor (CAR) T-cell class of therapy is also associated with the risks of CRS and neurologic toxicity including ICANS. On March 14, 2024, the Breyanzi (lisocabtagene maraleucel) REMS was modified to remove training requirements to minimize the burden on the healthcare delivery system of complying with the REMS. This modification is one product in the class modification of REMS for BCMA- or CD 19-directed genetically modified autologous T-cell immunotherapies. Part of the rationale for this class-wide modification includes the availability of non-REMS training materials developed by professional societies.[13] We are also encouraged that information about these risks are making their way into professional guidelines and educational materials that are available to the broader prescribing population for hematology and oncology.

The REMS Oversight Committee (ROC) was informed that the review team concluded a REMS is not necessary to ensure the benefits of tarlatamab outweighs its risks for the treatment of ES-SCLC. The ROC agreed with the review team's rationale and decision by stating, "The rates of CRS and neurotoxicity including ICANS are of low grade and similar to other BiTE drug products approved without a REMS. In addition, stakeholders expected to prescribe/administer this drug are likely to be familiar with the potential risks of CRS and neurotoxicity including ICANS and how to monitor for and manage them should they occur."

If approved, the risks of tarlatamab will be conveyed through labeling. To better understand postmarketing safety, tarlatamab will have enhanced pharmacovigilance. Additionally, a PMR will be issued to conduct an integrated safety analysis of data from patients with extensive stage small cell lung cancer to further characterize the long-term incidence, severity, and outcome of the known serious risks of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and neurologic toxicity. This PMR is intended to provide additional safety information that is needed to support the safety of the product.[7]

DRM recommends that, should tarlatamab be approved, a REMS is not necessary to ensure its benefits outweigh its risks for the treatment ES-SCLC.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with tarlatamab use are well documented. Should DO2 have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

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