Tarlatamab-dlle (IMDELLTRA)
National Drug Monograph
October 2024

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Tarlatamab is a bispecific delta-like ligand 3 (DLL3)-directed CD3 T-cell engager.
- Tarlatamab binds to DLL3 antigens on cell surfaces including tumor cells, and to the CD3 receptors on T-cells. This activates the T-cells to release inflammatory cytokines and lyse DLL3 expressing cells.

Indication(s) Under Review in This Document

- Extensive-stage small cell lung cancer (ES-SCLC) in adult patients with disease progression on or after platinum-based chemotherapy (granted accelerated approval)[1,2]

Dosage Form(s) Under Review

- Dosage Forms and Strengths[1]
  - 1 mg in a single-dose vial
  - 10 mg in a single-dose vial
- Dosing

Tarlatamab Dosage and Schedule Recommendations*				
Schedule (Cycle)	Day	Dose	Administration	Monitoring***
Cycle 1 (step-up dosing)	Day 1**	1 mg	1-hour intravenous (IV) infusion in an appropriate healthcare setting	Monitor for 22 to 24 hours from the start of infusion Recommend patients stay within 1-hour of an appropriate healthcare setting accompanied by a caregiver for 48 hours from the start of infusion
	Day 8**	10 mg		
	Day 15	10 mg		6 to 8 hours post infusion
Cycle 2	Day 1 and 15	10 mg		6 to 8 hours post infusion
Cycles 3 and 4	Day 1 and 15	10 mg		3 to 4 hours post infusion
Cycle 5 and onward	Day 1 and 15	10 mg		2 hours post infusion

*Each cycle is 28-days

**Concomitant medications dexamethasone and normal saline should be administered before and after tarlatamab

***If patients experience Grade ≥2 cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) or neurological toxicity during prior treatments, monitoring should be extended

- Administration
  - Tarlatamab is administered intravenously over one hour at a constant flow rate using an infusion pump.
  - Only a qualified healthcare professional with appropriate medical support who is able to manage severe reactions such as CRS and ICANS should administer tarlatamab.
  - It is recommended to administer concomitant medications before and after Cycle 1 to reduce the risk of CRS reactions.
    - Dexamethasone 8 mg IV (or equivalent)
      - Days 1 and 8: within one hour prior to tarlatamab administration
    - Normal saline 1 liter IV over 4-5 hours
      - Days 1, 8, and 15: immediately after completion of tarlatamab administration

Clinical Evidence Summary

Efficacy Considerations

- The efficacy of tarlatamab for recurrent or relapsed ES-SCLC was evaluated as part of a phase 1 trial, DeLLphi-300, that showed promising antitumor activity. The phase 2 DeLLphi-301 trial then resulted in durable objective responses and promising survival outcomes in this patient population.[3]
- Efficacy data are summarized in Table 1.

Table 1: Efficacy results from DeLLphi-301 and DeLLphi-300

Study	Design	Results

DeLLphi-301[3]	**Phase 2**, open-label, international trial
	
	Inclusion: adults ≥18 years old, histologically or cytologically confirmed SCLC, recurrent/relapse of disease after one platinum-based treatment and at least one other line of therapy, ≥1 measurable lesion, ECOG PS 0-1
	
	Exclusion: untreated or symptomatic brain
		Demographics: similar at baseline except higher percentage of brain metastases in 100 mg tarlatamab group
		
		Results
		• 10-mg dose selected for parts 2 and 3
		  ○ Part 1: n=176 (10-mg + 100-mg)
		  ○ Part 2: n=100 (10-mg)
		  ○ Part 3: n=34 (10-mg)
		• Median follow-up time: 10.6 months for 10 mg group and 10.3 months for 100 mg group
		• Tarlatamab 10-mg: n=100
		• Tarlatamab 100-mg: n=88

<table>
<tr>
<td></td>
<td>metastases, interstitial lung disease

Methods
• Part 1: dose comparison assessment (10 mg vs. 100 mg IV over 60 minutes)
• Part 2: enrollment of 100 patients at selected dose
• Part 3: safety assessment when inpatient monitoring during Cycle 1 was reduced from 48 to 24 hours after infusion

Interventions
• Cycle 1, Day 1: 1 mg IV tarlatamab (step up dose)
• Cycle 1, Day 8 and 15: selected target dose (either 10 mg or 100 mg IV)
• Cycle 2 and onward, Day 1 and 15: selected target dose
• Every 28-day cycles until progression of disease
• Dexamethasone 8 mg IV on Cycle 1, Day 1 and 8 before tarlatamab
• Normal saline 1 liter IV on Cycle 1, Day 1,8,15 after tarlatamab</td>
<td>Primary Endpoint: objective response rate (ORR) - complete or partial response, as assessed by blinded independent central review
<table>
<tr><th>Endpoint</th><th>10-mg</th><th>97.5% CI</th><th>100-mg</th><th>97.5% CI</th></tr>
<tr><td>ORR (%)</td><td>40</td><td>29-52</td><td>32</td><td>21-44</td></tr>
</table>
• Complete response was seen in 2% of patients
• Partial response was seen in 38% of patients

Secondary Endpoints: median duration of objective response (mDOR); disease control (DC); median duration of disease control (DODC); median progression-free survival (mPFS); median overall survival (OS); adverse events; serum concentration of tarlatamab; formation of anti-tarlatamab antibody
<table>
<tr><th>Endpoint</th><th>10-mg</th><th>95% CI</th><th>100-mg</th><th>95% CI</th></tr>
<tr><td>mDOR (months)</td><td>NE</td><td>5.9-NE</td><td>NE</td><td>6.6-NE</td></tr>
<tr><td>DC (%)</td><td>70</td><td>60-79</td><td>63</td><td>52-73</td></tr>
<tr><td>mDODC (months)</td><td>6.9</td><td>5.4-9.7</td><td>6.7</td><td>4.2-NE</td></tr>
<tr><td>mPFS (months)</td><td>4.9</td><td>2.9-6.7</td><td>3.9</td><td>2.6-4.4</td></tr>
<tr><td>mOS (months)</td><td>14.3</td><td>10.8-NE</td><td>NE</td><td>12.4-NE</td></tr>
</table>
NE: not estimable</td>
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<tr>
<td>Extended follow-up at 13.6 months[4]</td>
<td colspan="2">
<table>
<tr><th>Endpoint</th><th>10-mg</th><th>95% CI</th></tr>
<tr><td>ORR (%)</td><td>40</td><td>30.3-50.3</td></tr>
</table>
• Complete response was seen in 3% of patients
• Partial response was seen in 37% of patients
<table>
<tr><th>Endpoint</th><th>10-mg</th><th>95% CI</th></tr>
<tr><td>mDOR (months)</td><td>9.7</td><td>6.8-NE</td></tr>
<tr><td>DC (%)</td><td>70</td><td>60-79</td></tr>
<tr><td>mDODC (months)</td><td>6.9</td><td>5.4-9.7</td></tr>
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mPFS (months)	4.3	2.9-5.6
mOS at 20.7 months (months)	15.2	10.8-NE

NE: not estimable

- 6-month PFS: 39.2%; 12-month PFS: 24.0%
- 18-month OS: 46%

Subgroup analysis[5]

- Efficacy analysis by the presence of brain metastases
- Tarlatamab 10 g every 2 weeks (N=100)

	Baseline brain metastases	
Baseline characteristic	**Yes (N=23)**	**No (N=77)**
ECOG PS 0/1, N (%)	4 (17) / 19 (83)	22 (29) / 55 (71)
Median number of prior lines of therapy (range)	2 (2-5)	2 (1-6)
Prior anti-PD-(L)1 treatment, N (%)	19 (83)	55 (71)
DLL3 expression (>0% of tumor cells), x/X (%)	21/22 (95)	59/61 (97)
Outcome		
ORR, % (95% CI)	52 (31-73)	38 (27-49)
mDOR, months (range)	NE (3 to 12+)	NE (2 to 12+)
DOR probability at 12 months, KM estimate, % (95% CI)	55 (22-78)	50 (29-68)
mPFS, months (95% CI)	6.7 (3-NE)	4.0 (3-6)
mOS, months (95% CI)	14.3 (14-NE)	NE (9-NE)

NE: not estimable

- Intracranial activity per mRANO BRAIN METASTASES Analysis
- Patients with baseline CNS lesions ≥10 mm

	10 mg (N=3)	100 mg (N=14)
CNS tumor shrinkage ≥30%, N (%)	10 (59%)	
Intracranial disease control, N (%)	16 (94%)	
Median duration of intracranial disease control, N (range)	NE (2.6 to 13.9+ months)	
CNS disease progression per modified RANO-BM, N (%)	3 (18%)	

DeLLphi-300 trial update[6]

- **Phase 1**, open-label study
- **Objective:** assess the safety, tolerability, and pharmacokinetics of tarlatamab
- Dose exploration (0.003-100 mg)
- Dose expansions (10-100 mg)
- Stratified by the presence of absence of brain metastases

Extended Follow-up (12.1 months)

- Tarlatamab ≥10 mg IV every 2 weeks, every 3 weeks, or once on day 1 and day 8 of a 21-day cycle

Efficacy:

Outcome	Tarlatamab every 2 weeks (N=17)
ORR (%)	35.5
mDOR, months, (95% CI)	14.9 (3.0-NE)
mOS, months (95% CI)	20.3 (5.1-NE)

NE: not estimable

Brain metastases:

Outcome	Brain metastases (N=46)	No brain metastases (N=136)

		ORR, N (%)	9 (19.6)	34 (25.0)
		DCR, N (%)	27 (58.7)	68 (50.0)
		mDOR, months(95% CI)	14.9 (3.8-NR)	13.0 (7.4-NR)
		mPFS, months (95% CI)	3.7 (1.9-4.8)	3.7 (1.9-5.3)
		mOS, months (95% CI)	13.2 (6.6-NR)	15.5 (10.6-NR)
		DCR: disease control rate; NR: not reached		

ECOG PS: Eastern Cooperative Oncology Group Performance Status; PD-(L)1: programmed cell death 1 protein/programmed cell death ligand-1 protein; KM: Kaplan Meier, CNS: central nervous system

- DeLLphi-301 evaluated the role of tarlatmab in patients with advanced SCLC previously treated with at least two lines of therapy. The median number of previous lines of therapy was two.
- Tarlatamab showed durable antitumor activity with an objective response rate of 40% and a median progression-free survival of 4.9 months at the 10-mg dose.
- When two active doses were compared for dose optimization, the 10-mg dose was selected for subsequent tarlatamab trials due to its more favorable response over the 100-mg dose.
- Extended follow-up at 13.6 months demonstrated sustained benefit with ORR of 40% and 6-month and 12-month PFS rates of 39.2% and 24.0%, respectively, compared to the initial analysis. Overall survival was found to be similar regardless of chemotherapy-free interval (<90 days vs $\geq$ 90 days since treatment).
- In a subgroup analysis, tarlatamab showed durable response regardless of whether treated, stable brain metastases were present at baseline.
    - Patients with previously treated (after radiotherapy) CNS lesions larger than 10mm demonstrated tumor shrinkage and intracranial disease control.
- Extended follow-up results of the phase 1 DeLLphi-300 trial showed potential survival and intracranial activity of tarlatamab.

Safety Considerations

Safety Results from Clinical Trials:

- The safety of tarlatamab monotherapy was evaluated in the DeLLphi-300 (phase I) and DeLLphi-301 (phase 2) trials including a pooled population of 187 patients with ES-SCLC.[1]
- Common adverse events (>20%) of any grade included CRS, fatigue, pyrexia, dysgeusia, decreased appetite, musculoskeletal pain, constipation, anemia, and nausea.
- Safety data are summarized in Table 2 below.

Table 2: Safety results from DeLLphi-300 and DeLLphi-301

Adverse Reaction	Any grade (%)	Grade 3 or 4 (%)
CRS	55	1.6
Fatigue	51	10
Pyrexia	36	0
Decreased appetite	34	2.7
Nausea	22	1.6
Constipation	30	0.5

Musculoskeletal pain	30	1.1
Anemia	27	6
Dyspnea	17	2.1
Cough	17	0
ICANS	9	-
Laboratory Abnormalities		
Decreased lymphocytes	84	57
Decreased hemoglobin	58	5
Decreased white blood cells	44	3.8
Decreased platelets	33	3.2
Decreased neutrophils	12	6
Decreased sodium	68	16
Decreased potassium	50	5
Increased aspartate amino transferase	44	3.2
Increased alanine aminotransferase	42	2.1
Decreased magnesium	33	1.6
Increased creatinine	29	0.5
Increased sodium	26	0
Increased alkaline phosphate	22	0

- **Boxed warnings:**
    - **CRS** (Cytokine Release Syndrome)
        - Serious or life-threatening response to the activation of T cells and/or other immune effector cells from immune therapy.
        - Signs and symptoms include pyrexia, hypotension, fatigue, tachycardia, headache, hypoxia, nausea, and vomiting.
        - Life-threatening complications of CRS include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).
        - In the pooled safety population, CRS occurred in 55% of patients. The breakdown of grading is below. Most CRS events were grade one.
            - Grade 1: 34%
            - Grade 2: 19%
            - Grade 3: 1.1%
            - Grade 4: 0.5%
        - CRS recurrence occurred in 24% of patients. The breakdown of grading is below.
            - Grade 1: 18%
            - Grade 2: 6%

        - The median time to onset of CRS of all grades was 13.5 hours after the most recent dose (range 1 to 268).
        - The median duration of CRS in DeLLphi-300 was 3 days and in DeLLphi-301 was 4 days.
        - CRS occurred the most after the first dose of tarlatamab, Cycle 1 Day 1 (43%)
            - CRS occurrence after the second dose, Cycle 1 Day 8: 29%
            - CRS occurrence after the third dose or later, Cycle 1 Day 15: 9%
        - At the first sign of CRS, tarlatamab should be discontinued with hospitalization and supportive care provided based on severity
    - **ICANS** (Immune Effector Cell-Associated Neurotoxicity Syndrome)
        - Serious or life-threatening neurotoxicity.
        - Signs and symptoms include confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia.
        - In the pooled safety population, ICANS occurred in 9% of patients.
        - ICANS recurrence occurred in 1.6% of patients.
        - The median time to onset of ICANS was 29.5 days after the first dose (range 1 to 154).
            - In the DeLLphi-301 study, the median time to onset of ICANS was 5 days after a dose during cycle 1.
        - The median time to resolution of ICANS was 33 days (range 1 to 93).
            - In the DeLLphi-301 study, the median time to resolution was 6.5 days.
        - ICANS occurred the most often after Cycle 2 Day 1 (24%).
            - In the DeLLphi-301 study, ICANS occurred more frequently in patients who received the 100 mg dose versus the 10 mg dose and presented most often after Cycle 1 Day 8 and Cycle 2 Day 1, respectively.
        - At the first sign of ICANS, tarlatamab should be held and patients should be evaluated and provided supportive care based on severity.
        - ICANS can occur concurrently with CRS, after CRS, or without CRS.
        - Patients should withhold from driving and completing activities requiring mental engagement such as operating heavy machinery until any neurological symptoms resolve.
- **Contraindications:** none
- **Other warnings / precautions**:
    - **Neurologic toxicity:** can cause serious or life-threatening neurotoxicity including ICANS. Monitor for signs and symptoms of neurologic toxicity during treatment. Tarlatamab should be withheld or permanently discontinued based on severity. Neurologic toxicity occurred in 47% of patients with 10% of patients having a grade three toxicity. The most common neurologic toxicities were headache, peripheral neuropathy, dizziness, insomnia, muscular weakness, delirium, syncope, and neurotoxicity in 14%, 7%, 7%, 6%, 3.7%, 2.1%, 1.6%, and 1.1% of patients, respectively.
    - **Cytopenias:** can cause neutropenia, thrombocytopenia, and anemia. Complete blood counts should be performed at baseline, prior to each dose, and as clinically

indicated. Tarlatamab may be temporarily withheld or permanently discontinued based on severity.
    - Decreased neutrophils were observed in 12% of patients, with grade three or four decreased neutrophils in 6% of patients. The median time to onset of grade three or four neutropenia was 29.5 days (range 2 to 213).
    - Decreased platelets were observed in 33% of patients, with grade three or four decreased platelets in 3.2% of patients. The median time to onset of grade three or four thrombocytopenia was 50 days (range 3 to 420).
    - Decreased hemoglobin was observed in 58% of patients, with grade three or four decreased hemoglobin in 5% of patients. Febrile neutropenia was observed in 0.5% of patients.
  - **Infections:** can cause serious infections, life-threatening, or and fatal infections. Patients should be monitored for signs and symptoms of infection at baseline, during treatment, and as clinically indicated. Based on severity, treatment may be withheld or permanently discontinued. Infections occurred in 41% of patients. Grade three or four infections occurred in 13% of patients. The most common infections were COVID-19, urinary tract infection, pneumonia, respiratory tract infection, and candida infections in 9%, 10%, 9%, 3.2%, and 3.2% of patients, respectively.
  - **Hepatotoxicity:** can cause hepatotoxicity. Liver enzymes and bilirubin should be monitored at baseline, prior to each dose, and as clinically indicated. Elevated ALT, AST, and bilirubin occurred in 42%, 44%, and 15% of patients, respectively. Grade three or four elevations in ALT, AST, and bilirubin were 2.1%, 3.2%, and 1.6% of patients, respectively.
  - **Hypersensitivity:** severe hypersensitivity reactions including rash and bronchospasm can occur. Patients should be monitored during treatment and managed as clinically indicated. Withhold treatment or permanently discontinue based on severity.
  - **Embryo-fetal toxicity:** may cause fetal harm. Females of reproductive potential should be advised to use effective contraception during treatment and for two months after the last dose due to the potential risk to a fetus.
- **Adverse reactions**
  - **Common (≥20%):** CRS, fatigue, pyrexia, dysgeusia, decreased appetite, musculoskeletal pain, constipation, anemia, and nausea
  - **Serious Adverse events / Deaths / Discontinuation:** In the pooled safety population, 58% of patients had a serious adverse reaction with CRS, pneumonia, pyrexia, and hyponatremia present in >3% of patients. Fatal adverse reactions occurred in 2.7% of patients including pneumonia, aspiration, pulmonary embolism, respiratory acidosis, and respiratory failure. Adverse reactions led to permanent discontinuation in 7% of patients and included CRS and tumor lysis syndrome in >1% of patients. In the DeLLphi-301 trial, one patient died due to respiratory failure related to treatment.

Other Considerations

- **PK/PD:** steady state exposures were observed by cycle 2 day 15 of treatment. The half-life of tarlatamab is 11.2 days (min 4.3, max 26.5).
- **Administration:** recommended pre- and post-medications should be administered for each dose of the first cycle. Treatment should be administered using an infusion pump over one hour through an IV catheter that has been flushed over 3-5 minutes with 0.9% sodium chloride for injection. Patients should be well hydrated prior to tarlatamab administration.
- **Special populations**
  - **Pregnancy:** may cause fetal harm. Females of reproductive potential should undergo pregnancy testing prior to treatment initiation and are recommended to use effective contraception during treatment and for two months after the last dose.
  - **Lactation:** the effects of drug exposure in a breastfed child are unknown and patients should be advised to avoid breastfeeding during treatment and for two months after the last dose.
  - **Pediatric use:** use has not been established in the pediatric population.
  - **Geriatric use:** no differences in pharmacokinetics and safety were observed between older patients (≥65 years) and younger patients.

Risk-Benefit Assessment (for Oncology NMEs only)

- **Outcome in clinically significant area: Objective Response Rate**
- **Effect Size: ORR 40% in 10 mg group; 32% in 100 mg group**
- **Potential Harms: ≥Grade 3 in 59%**
- **Net Clinical Benefit: Not Available**

Other Therapeutic Options

Alternative treatments for ES-SCLC are listed in table 3 below.

Table 3 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Topotecan[7,8,9]	Oral: NF IV: PA-F	Indication: relapsed or progressive platinum-sensitive SCLC at least 60 days after first-line chemotherapy initiation Efficacy: • Randomized comparative trial • T (topotecan) IV (N=107) vs. CAV (cyclophosphamide, doxorubicin, vincristine) IV every 21 days (N=104) • Patients with progressive disease at least 60 days after completing	Dosing • IV: 1.5 mg/m2/day for 5 days every 21 days • Oral (PO): 2.3 mg/m2/day for 5 days every 21 days for at least 4 cycles Monitoring • CBC, renal panel, bilirubin

		first-line chemotherapy with at least one measurable lesion, ECOG PS 0-2, adequate organ function and blood counts, and without symptomatic brain metastases **T** vs. **CAV** ORR (%): **24** (16-32) vs. **18** (11-26) mDOR (mo): **3.3** (3-4.1) vs. **3.5** (3-5.3) mTTP (mo): **3.1** (2.6-4.1) vs. **2.8** (2.5-3.2); HR 0.92, 95% CI (0.69-1.22) mOS (mo): **5.8** (4.7-6.8) vs. **5.7** (5-7); HR 1.04, 95% CI (0.78-1.39) • Most common grade 3/4 hematologic ADE: neutropenia, leukopenia, thrombocytopenia, anemia • Most common grade 3/4 non-hematologic ADE: alopecia, fatigue, GI toxicities (nausea, vomiting, anorexia) • Phase 3, randomized trial • Oral T (topotecan) (N=71) vs. BSC (best supportive care) (N=70) • Adult patients with extensive or limited SCLC unsuitable for further IV chemotherapy, one prior chemotherapy regimen, ECOG PS 0-2, adequate organ function and blood counts, no symptomatic CNS metastases **T** vs. **BSC** mOS (wks): **25.9** (18.3-31.6) vs. **13.9** (11.1-18.6); P=0.0104 • Most common grade 3/4 hematological ADE: neutropenia, thrombocytopenia, anemia • Open-label, randomized, phase 3 study • PO topotecan (N=153) vs. IV topotecan (N=151) • Adult patients with limited or extensive stage SCLC with	Drug-drug interactions • No formal studies reported Adverse effects • Boxed warning: bone marrow suppression • Nausea, alopecia, vomiting, diarrhea, constipation, fatigue, pyrexia • Interstitial lung disease, extravasation and tissue injury, embryo-fetal toxicity Clinical pearls • Neutrophils should be ≥1500 cells/mm3 • Platelets should be ≥100,000/mm3

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<td>response to first-line therapy with recurrence after ≥90 days, one prior chemotherapy treatment, ECOG 0-2, adequate organ function and blood counts, CNS metastases (only if asymptomatic without steroids)
<table>
<tr><td></td><td>PO</td><td>95% CI</td><td>IV</td><td>95% CI</td></tr>
<tr><td>ORR(%)</td><td>18.3</td><td>12.2-24.4</td><td>21.9</td><td>15.3-28.5</td></tr>
<tr><td>mTTR (wks)</td><td>6.1</td><td>4.4-17.7</td><td>6.1</td><td>2.1-13.9</td></tr>
<tr><td>mDOR (wks)</td><td>18.3</td><td>9-65.4</td><td>25.4</td><td>8.4-132.1</td></tr>
<tr><td>mST (wks)</td><td>33</td><td>29.1-42.4</td><td>35</td><td>31-37.4</td></tr>
</table>

Most common grade 3/4 hematological toxicities: neutropenia, thrombocytopenia, anemia
Most common grade 3/4 non-hematological toxicities: nausea, alopecia, fatigue, diarrhea

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<td>Lurbinectedin[10]</td>
<td>F (CFU)</td>
<td>Indication: subsequent therapy in metastatic SCLC

Efficacy:

Phase 2, single-arm, open-label, basket trial
N=105, received lurbinectedin (L)
Adult patients with proven diagnosis of SCLC, measurable disease, absence of brain metastases, adequate organ function, and only one pretreatment with chemotherapy-containing regimen
Median follow-up: 17.1 months

<table>
<tr><td></td><td>L</td><td>95% CI</td></tr>
<tr><td>ORR (%)</td><td>35.2</td><td>26.2-45.2</td></tr>
<tr><td>mDOR (months)</td><td>5.3</td><td>4.1-6.4</td></tr>
<tr><td>mPFS (months)</td><td>3.5</td><td>2.6-4.3</td></tr>
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Chemotherapy-free interval <90 days: ORR 22.2% (95% CI 11.2-37.1)

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<td>Dosing

3.2 mg/m2 IV every 21 days until disease progression or unacceptable toxicity

Monitoring

CBC, LFTs, CPK

Drug-drug interactions

Strong CYP3A inhibitors and inducers

Adverse effects

Bone marrow suppression, hepatotoxicity, constipation, diarrhea, nausea, vomiting, decreased appetite, increased serum glucose, fatigue, musculoskeletal pain,

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		• Chemotherapy-free interval ≥90 days: ORR 45% (95% CI 32.1-58.4) • Most common grade 3-4 adverse events: anemia, leukopenia, neutropenia, thrombocytopenia • Serious adverse events: 10% • Treatment-related deaths: 0	increased serum creatinine Clinical pearls • Neutrophils should be ≥1500 cells/mm3 • Platelets should be ≥100,000/mm3

NF: non-formulary; PA-F: prior authorization-formulary; mTTP: median time to progression; mTTR: median time to response; mST: median survival time; F: formulary; CFU: criteria for use; CBC: complete blood counts; LFT: liver function tests; CPK: creatinine phosphokinase

Projected Place in Therapy

- Lung cancer is the second most common cancer in the United States associated with 1 in 5 cancer deaths.[11]
- SCLC encompasses about 10-15% of all lung cancers and the 5-year relative survival rate between 2012 and 2018 was 7%.[12]
- Between 2010 and 2017, the Veterans Affairs Central Cancer Registry reported a total number of 54,922 Veterans diagnosed with lung cancer.[13]
  - A small cell histology was classified in 12.9% of Veterans. The median overall survival was 8 to 9 months and the 3-year overall survival rate increased from 9.1% to 12.3%.
- Limited treatment options in relapsed SCLC are based on whether the cancer is chemo-sensitive (chemotherapy-free interval >6 months) or chemo-resistant (chemotherapy-free interval ≤6 months).
- Tarlatamab is a bispecific DLL3-directed CD3 T-cell engager that was studied in the phase 2 DeLLphi-301 trial in patients with recurrent or relapsed ES-SCLC after one platinum-based treatment and at least one other line of therapy. Outcomes were notable for an ORR of 40% and a PFS benefit of 4.9 months at the 10-mg dose. The drug was granted accelerated approval in 2024.
- DeLLphi-301 also included patients with asymptomatic treated stable brain metastases (23%), which is a common concern for patients with SCLC. An extended follow-up of the study showed sustained benefit in ORR and PFS. A subgroup analysis evaluating efficacy in patients with or without baseline brain metastases demonstrated durable response in both populations and for those with larger CNS lesions with prior radiotherapy treatment, tarlatamab demonstrated CNS tumor shrinkage.
- Based on the available studies, tarlatamab's potential place in therapy may be after failing first-line chemotherapy and an initial subsequent line of therapy.
- Per the NCCN guidelines, tarlatamab is not a preferred agent in patients who are chemo-sensitive and is listed as another recommended regimen after re-treatment with a first-line platinum-based doublet. In chemo-resistant disease, tarlatamab is listed as a preferred regimen along with lurbinectedin and topoisomerase inhibitors (topotecan, irinotecan).[14]
- The VA Clinical Pathways also stratify patients based on if disease progression occurred within 6 months or more than 6 months later.[15]
  - Tarlatamab is recommended for patients with a good performance status (PS 0-1) who have failed retreatment with a platinum-based doublet (if chemo-sensitive) and lurbinectedin.
- Tarlatamab has not been directly compared to other subsequent therapies. However, indirect comparisons may indicate higher ORR compared to topotecan and similar response rates to lurbinectedin.
- Of note, the toxicity profile includes CRS, fatigue, pyrexia, dysgeusia, decreased appetite, musculoskeletal pain, constipation, anemia, nausea, and other laboratory abnormalities.
- Due to the risk of CRS and ICANS which have occurred most frequently in the first two cycles of treatment, patients require specific monitoring and pre-medications before and after the first few doses.
- The estimated cost of tarlatamab is ~$1,100.00 for one 1-mg vial and ~$11,00.00 for one 10-mg vial bringing the total cost for 5 cycles of treatment to be ~$111,100.00.
  - Lurbinectedin treatment for 5 cycles is estimated to be ~$50,000.00.
  - Topotecan treatment for 5 cycles is estimated to be ~$30,000.00 for oral administration and ~$1,300.00 for IV administration.
- Due to the accelerated approval, recommendations are based on ORR and may not be sufficient to confirm survival benefit. However, in a cancer with limited therapies, tarlatamab is a considerable option in relapsed disease among other subsequent therapies. Given the expense and safety issues of the drug, it is reasonable to treat patients with either lurbinectedin or topotecan initially before administering tarlatamab. Ongoing phase 3 studies will be useful in establishing survival benefit.

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Appendix A. Acquisition Prices and Cost Considerations

Refer to VA pricing sources for updated information