Up Close with Tarlatamab

This section provides an overview of tarlatamab-dlle (IMDELLTRA™).

- 🏷️ Indications
- 💊 Dosing and Administration
- ⚠️ CRS
- 🧠 Neurotoxicity (including ICANS)
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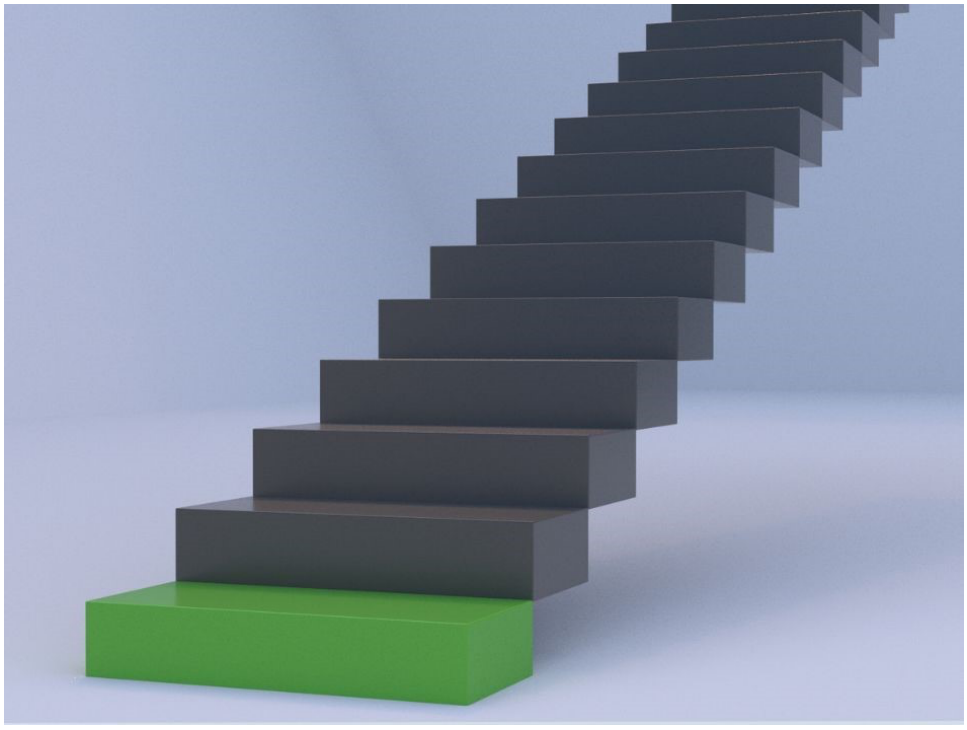
🏷️ Indications

Tarlatamab is a **bispecific delta-like ligand 3 (DLL3)-directed CD3 T-Cell engager** indicated for the treatment of adult patients with:

- **Extensive stage small cell lung cancer (ES-SCLC)** with **disease progression on or after platinum-based chemotherapy**

Note: These indications are approved under accelerated approval based on response rate and durability of response. Continued approval may be contingent upon verification of clinical benefit in confirmatory trials.

💊 Dosing and Administration



Tarlatamab is administered via an **intravenous (IV) infusion over 1-hour** (rate of 250 mL/hour) with unique **step-up dosing** only during Cycle 1 (Days 1, 8, and 15) to reduce the risk and severity of cytokine release syndrome (CRS) as shown below.

Dosing Schedule	Day of Treatment	Tarlatamab Dose/ Route		Administration Instructions	Tarlatamab Monitoring Recommendations
Cycle 1 (Step-Up)[a]	Day 1	Step-up Dose 1	1 mg IV	Administer over a 1-hour infusion at an appropriate healthcare setting.	Monitor patients from the start of infusion for 22 to 24 hours on 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 accompanied by a caregiver.
	Day 8	10 mg IV			
	Day 15	10 mg IV			Observe patients for 6-8 hours post infusion.[b]
Cycle 2	Day 1	10 mg IV		Administer over a 1-hour infusion at an appropriate healthcare setting.	Observe patients for 6-8 hours post infusion.[b]
	Day 15	10 mg IV			
Cycles 3-4	Day 1	10 mg IV		Administer over a 1-hour infusion at an appropriate healthcare setting.	Observe patients for 3-4 hours post infusion.[b]
	Day 15	10 mg IV			

Cycles 5+	Day 1	10 mg IV	Administer over a 1-hour infusion at an appropriate healthcare setting.	Observe patients for hours post infusion.[b]
	Day 15	10 mg IV		

[a]Administer concomitant medication before and after tarlatamab infusion **(Cycle 1 only)**

- Prior to tarlatamab infusion (Cycle 1 Days 1 and 8):
  - Administer 8 mg of dexamethasone intravenously (or equivalent) within 1 hour of tarlatamab infusion
- Post-tarlatamab infusion (Cycle 1 Days 1, 8, 15):
  - Administer 1 liter of normal saline intravenously over 4-5 hours immediately following completion of tarlatamab infusion

[b]Extended monitoring in a healthcare setting is not required unless the patient experiences Grade ≥ 2 CRS, ICANS or neurological toxicity during prior treatments

Recommendations for Restarting Tarlatamab Following Dose Delay

Last Administered Cycle/Day of Tarlatamab	Last Dose of Tarlatamab Administered	Time Since Last Administered Dose of Tarlatamab	Recommended Action[a]
Cycle 1 Day 1	1 mg	≤ 14 days	Administer tarlatamab 10 mg, then resume the treatment plan as scheduled.
		> 14 days	Administer tarlatamab step-up dose 1 mg. If dose is tolerated, increase to 10 mg (one week later) and resume treatment plan as scheduled.
Cycle 1 Day 8	10 mg	≤ 21 days	Administer tarlatamab 10 mg, then resume the treatment plan as scheduled.
		> 21 days	Administer tarlatamab step-up dose 1 mg. If dose is tolerated, increase to 10 mg (one week later) and resume treatment plan as scheduled.
Cycle 1 Day 15 **and** Subsequent cycles every 2 weeks thereafter	10 mg	≤ 28 days	Administer tarlatamab10 mg, then resume the treatment plan as scheduled.
		> 28 days	Administer tarlatamab step-up dose 1 mg. If dose is tolerated, increase to 10 mg (one week later) and resume treatment plan as scheduled.

[a]Administer concomitant medication before and after tarlatamab infusion **(Cycle 1 only)**

- Prior to tarlatamab infusion (Cycle 1 Days 1 and 8):
  - Administer 8 mg of dexamethasone intravenously (or equivalent) within 1 hour of tarlatamab infusion
- Post-tarlatamab infusion (Cycle 1 Days 1, 8, 15):
  - Administer 1 liter of normal saline intravenously over 4-5 hours immediately following completion of tarlatamab infusion

[b]Extended monitoring in a healthcare setting is not required unless the patient experiences Grade ≥ 2 CRS, ICANS or neurological toxicity during prior treatments

⚠️ CRS

What is it? Cytokine release syndrome (CRS) is a systemic inflammatory response that can occur when the immune system is activated and releases large amounts of cytokines—proteins that help regulate immune responses.

- **Signs and symptoms:** pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia.
- CRS is frequently graded using the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria.

Why it matters. CRS occurred in **55%** of patients who received tarlatamab in the studies DeLLphi-300 and DeLLphi-301.

- Most CRS events occurred during **Cycle 1**, with the highest events occurring with the first dose of tarlatamab (43%), followed by the second dose (29%) and third or subsequent doses (9%).
    - **≥ Grade 2 CRS events** occurred on the following days of Cycle 1
        - Day 1 (16%)
        - Day 8 (4.3%)
        - Day 15 (2.1%)
    - CRS events were primarily Grade 1 (34%) with Grade 3 and 4 events occurring in 1.1% and 0.5% of patients, respectively.
- The **median time to onset** of CRS following administration of the most recent dose of tarlatamab was 13.5 hours (range: 1 to 268).
    - The median time to onset of ≥ Grade 2 CRS events following administration of the most recent dose of tarlatamab was 14.6 hours (range: 1 to 566).

- Care teams should monitor patients for signs/symptoms of CRS during treatment with tarlatamab.
    - **At first sign of CRS**, care teams should **immediately discontinue the tarlatamab infusion** and evaluate the patient for need of hospitalization and supportive care measures.

The bottom line. CRS was primarily low-grade and predictable throughout Cycle 1 and for subsequent cycles.

🧠 Neurotoxicity (including ICANS)

What is it? Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) is characterized by various neurological symptoms resulting from the activation of the immune system and the resultant inflammatory processes.

- **Signs and symptoms:** encephalopathy, headaches, seizures, aphasia, motor deficits, ataxia, and tremor.
- ICANS is frequently graded using the ASTCT consensus criteria.

Why it matters. Neurological toxicity, including ICANS occurred in **47%** of patients in a pooled analysis of the two clinical trials, **10%** of which were reported as **Grade 3.**

- **Neurological toxicity consistent with ICANS** was reported in **9%** of patients treated with tarlatamab, including **recurrent** events in **1.6%** of patients.

    - ≥ Grade 2 CRS events occurred on the following days of Cycle 1: Day 1 (16%), Day 8 (4.3%), and Day 15 (2.1%); however, most patients experienced ICANS after receiving tarlatamab on Cycle 2 Day 1 (24%).
- The **median time to onset** of ICANS following administration of the **first** dose of tarlatamab was **29.5 days** (range: 1 to 154), though it can occur at any point several weeks following its administration.
- The **median time to resolution** of ICANS was **33 days** (range: 1 to 93).
- Care teams should advise their patients to avoid driving or operating heavy machinery in the event of any neurological symptoms, until these events resolve.
    - Tarlatamab **may need to be withheld or permanently discontinued based on the severity**.

The bottom line: The majority of ICANS events occurred on Day 1 of the second cycle, however events that occurred during the first cycle were of a higher grade.

🚨 Other Toxicities

Tarlatamab may cause other adverse reactions such as **cytopenias, infections, hypersensitivity, and certain toxicities including hepato- and embryo-fetal toxicity**.

Why it matters. In addition to the risks of CRS and neurotoxicity (including ICANS), care teams need to be on the lookout for other **tarlatamab-**associated toxicities.

Infections. Tarlatamab may cause serious and fatal infections.

- **Serious infections**, including opportunistic infections, occurred in **41%** of patients with **Grade 3 or 4** infections reported in **13%** of patients.
    - The most common serious infections reported were COVID-19 (of note, this trial was conducted during the COVID-19 pandemic), candida infections, pneumonia, and urinary tract infections.

The bottom line. Care teams should monitor patients for signs of infection before and during treatment; treat appropriately.

- **Based on severity**, tarlatamab **may need to be withheld or permanently discontinued**.

Cytopenias. Tarlatamab may cause cytopenias which include: thrombocytopenia, anemia, and neutropenia.

- In the pooled safety analysis, laboratory abnormalities resulted in **neutropenia (12%), anemia (58%), and thrombocytopenia (33%)** of patients who received tarlatamab.
    - These events do include **Grade 3 or 4 reductions** for neutropenia, anemia, and thrombocytopenia as followed: **6%, 5%, and 3.2%**.
- **Febrile neutropenia** occurred in **0.5%** of patients.

The bottom line. Care teams should **perform complete blood counts prior to treatment with each dose of tarlatamab and as clinically indicated** throughout treatment.

- **Withhold or discontinue** tarlatamab **based on neutropenia severity**.

Hepatoxicity. Tarlatamab may cause hepatotoxicity which can include in liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and markers like total bilirubin.

- Within the two clinical trials, **liver enzyme elevations, AST and ALT** were observed in **44%** and **42%** of patients and **total bilirubin elevations** occurred in **15%** of patients who received tarlatamab.
    - In addition, **Grade 3 or 4 AST** elevations occurred in **3.2%** of patients whereas **Grade 3 or 4 ALT elevations** occurred in **2.1%** of patients.
    - **Grade 3 or 4 total bilirubin elevations** occurred in **1.6%** of patients.

The bottom line. Care teams should **monitor liver enzymes routinely**, including AST/ALT/total bilirubin/total bilirubin prior to initiation of tarlatamab and during therapy.

- **Treatment with tarlatamab** may need to be **temporarily held or permanently discontinued based on severity**.

Hypersensitivity. Tarlatamab may cause severe hypersensitivity reactions, including but not limited to rash or bronchospasms.

The bottom line. Care teams should **monitor their patients for any sign/symptoms of hypersensitivity** during treatment with taralatamab.

- Care teams may need to **consider a temporary hold or permanent discontinuation based on severity**.

Embryo-Fetal Toxicity. Tarlatamab may cause fetal harm when administered to a pregnant woman.

- Advise **females of reproductive potential** to use effective contraception **during treatment** and **for at least 2 months** after the last dose.
- Verify pregnancy status before initiating tarlatamab.

Use in Specific Populations

- **Lactation:** Advise women not to breastfeed during treatment and for **2 months** after the last dose.
- **Pediatric Use:** The safety and efficacy of tarlatamab has not yet been established in the pediatric population.
- **Geriatric Use:** Of the total number of tarlatamab treated patients in these studies, 54% were 65 years of age and older and 12% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

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References:

1. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758.
2. IMDELLTRA™ (tarlatamab-dlle) [package insert]. Amgen Inc. Thousand Oaks, CA. 2024.

3. Paz-Ares L, Goldman JW, Goto K, et al. Tarlatamab, a first-in-class DLL3-targeted bispecific T-cell engager, in recurrent small-cell lung cancer: an open-label, phase I study. *J Clin Oncol.* Published online 2024. doi:10.1200/JCO.23.XXXXX.
4. Ganti AK, Shuster D, Schneider BJ, et al. Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med.* Published online 2024. doi:10.1056/NEJMoaXXXXX.