IMDELLTRA® (tarlatamab) powder for solution for infusion, 1mg/Vial & 10mg/Vial

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IMDELLTRA is 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

- Administer IMDELLTRA according to the step-up dose and schedule in Table 1 to reduce the incidence and severity of cytokine release syndrome (CRS) *[see Dosage and Administration (2.2)]*.
- Evaluate complete blood count, liver enzymes and bilirubin prior to administration of all doses of IMDELLTRA up through Cycle 5 Day 15 and then prior to administration of IMDELLTRA on Day 1 of each cycle starting with Cycle 6. More frequent evaluation may be necessary if clinically indicated *[see Warnings and Precautions (5.3, 5.5)]*.
- Ensure patients are well hydrated prior to administration of IMDELLTRA *[see Warnings and Precautions (5.1)]*.
- For Cycle 1, administer recommended concomitant medications in Table 3 before and after Cycle 1 Day 1 and Cycle 1 Day 8 IMDELLTRA infusions to reduce the risk of CRS reactions *[see Dosage and Administration (2.3)]*.
- IMDELLTRA 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) *[see Warnings and Precautions (5.1, 5.2)]*.
- Due to the risk of CRS and neurologic toxicity, including ICANS, 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 *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1, 5.2)]*.
- Recommend patients to remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA following Cycle 1 Day 1 and Cycle 1 Day 8 doses, accompanied by a caregiver.
- Inform both the patient and the caregiver on the signs and symptoms of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) prior to discharge.

2.2 Recommended Dosage and Administration

- Administer IMDELLTRA as an intravenous infusion for one hour.

- The recommended step-up dose and schedule for IMDELLTRA is provided in Table 1. Administer step-up dose and schedule on Cycle 1 Day 1 to reduce the incidence and severity of CRS.
- After step-up dose and schedule on Cycle 1 Day 1, administer IMDELLTRA every 2 weeks until disease progression or unacceptable toxicity.

Table 1. Recommended Dose and Schedule of IMDELLTRA

Dosing Schedule	Day	Dose of IMDELLTRA	Administration Instructions	Recommended Monitoring
Step-up Dose and Schedule Cycle 1	Day 1[a]	Step-up dose[a] 1 mg	Administer IMDELLTRA as a 1-hour intravenous infusion in an appropriate healthcare setting.	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 IMDELLTRA infusion accompanied by a caregiver.
	Day 8[a]	10 mg[a]		
	Day 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion[b]
Cycle 2	Day 1 and 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion[b].
Cycles 3 and 4	Day 1 and 15	10 mg		Observe patients for 3-4 hours post IMDELLTRA infusion[b].
Cycle 5 and subsequent infusions	Day 1 and 15	10 mg		Observe patients for 2 hours post IMDELLTRA infusion[b].

[a.] Administer recommended concomitant medications before and after Cycle 1 Day 1 and Cycle 1 Day 8 IMDELLTRA infusions as described in Table 3.

[b.] 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 for monitoring recommendations.

Note: See Table 4 for recommendation on restarting IMDELLTRA after dose delays.

Administration

- The intravenous (IV) catheter for concomitant medications administration can be used to administer the IMDELLTRA infusion.
- To ensure patency, flush the IV catheter over 3 to 5 minutes using 0.9% Sodium Chloride for Injection.
- Administer the reconstituted and diluted IMDELLTRA as a 1-hour intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm. Flush the IV-line upon completion of the IMDELLTRA infusion.

Table 2 provides the infusion duration and rate.

Table 2. IMDELLTRA Infusion Duration and Rate

Infusion Duration for 250 mL IV Preparation	Infusion Rate
1 hour	250 mL/hour

2.3 Recommended Concomitant Medications for IMDELLTRA Administration for Cycle 1 Day 1 and Cycle 1 Day 8

Administer recommended concomitant medications for IMDELLTRA during Cycle 1 Day 1 and Cycle 1 Day 8 as presented in Table 3 to reduce the risk of CRS *[see Warnings and Precautions (5.1)]*.

Table 3. Recommended Concomitant Medications for IMDELLTRA Administration for Cycle 1 Day 1 and Cycle 1 Day 8

Treatment Day	Medication	Administration
Cycle 1 Day 1 and Cycle 1 Day 8	Administer dexamethasone 8 mg intravenously (or equivalent)	Within 1 hour prior to IMDELLTRA administration
	Administer 1 liter of normal saline intravenously over 2 to 4 hours	Immediately after completion of IMDELLTRA infusion

2.4 Restarting IMDELLTRA After Dosage Delay

If a dose of IMDELLTRA is delayed, restart based on the recommendation as listed in Table 4 and resume the dose and schedule accordingly *[see Dosage and Administration (2.2)]*.

Administer recommended concomitant medications as indicated in Table 3.

Table 4. Recommendations for Restarting IMDELLTRA After Dosage Delay

Last Dose Administered	Time Since the Last Dose Administered	Action[a]
1 mg on Cycle 1 Day 1	2 weeks or less (≤ 14 days)	Administer IMDELLTRA 10 mg, then resume with the planned dose and schedule.
	Greater than 2 weeks (> 14 days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dose and schedule.
10 mg on Cycle 1 Day 8	3 weeks or less (≤ 21 days)	Administer IMDELLTRA 10 mg, then resume with the planned dose and schedule.
	Greater than 3 weeks (> 21 days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dose and schedule.

Last Dose Administered	Time Since the Last Dose Administered	Action[a]
10 mg on Cycle 1 Day 15 and subsequent Cycles every 2 weeks thereafter	4 weeks or less (≤ 28 days)	Administer IMDELLTRA 10 mg, then resume with the planned dose and schedule.
	Greater than 4 weeks (> 28 days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dose and schedule.

a. Administer recommended concomitant medications before and after Cycle 1 Day 1 and Cycle 1 Day 8 IMDELLTRA infusions and monitor patients accordingly *[see Dosage and Administration (2.1, 2.2 and 2.3)]*.

2.5 IMDELLTRA Dosage Modifications and Adverse Reaction Management

No dose reduction for IMDELLTRA is recommended. See Table 5 and Table 6 for recommended management of CRS, neurologic toxicity including ICANS respectively and Table 7 for cytopenias, infections and other adverse reactions.

Cytokine Release Syndrome (CRS)

Diagnose CRS based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypoxia, and hypotension.

If CRS is suspected, manage according to the recommendations in Table 5. Monitor patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygen) with continuous cardiac telemetry and pulse oximetry.

For severe or life-threatening CRS, recommend administering tocilizumab or equivalent therapy and intensive monitoring (e.g., ICU) for supportive therapy. Perform laboratory testing to monitor for disseminated intravascular coagulation (DIC), hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function. Table 5 provides the guidelines for grading and dosage modification and management of cytokine release syndrome.

Table 5. Guidelines for Grading and Dosage Modification and Management of Cytokine Release Syndrome[a]

CRS Grade	Defining Symptoms	IMDELLTRA Dosage Modification	Management
Grade 1	Symptoms require symptomatic treatment only (e.g., fever ≥ 100.4°F without hypotension or hypoxia).	Withhold IMDELLTRA until event resolves, then resume IMDELLTRA at the next scheduled dose[b].	• Administer symptomatic treatment (e.g., acetaminophen) for fever. • Consider dexamethasone 4 mg to 10 mg oral or IV (or equivalent)[c].
Grade 2	Symptoms require and respond to moderate intervention. Fever ≥ 100.4°F, • Hypotension responsive to fluids not requiring vasopressors and/or • Hypoxia requiring low flow nasal cannula or blow-by.	Withhold IMDELLTRA until event resolves, then resume IMDELLTRA at the next scheduled dose[b].	• Recommend hospitalization for a minimum of 24 hours with cardiac telemetry and pulse oximetry. • Administer symptomatic treatment (e.g., acetaminophen) for fever. • Administer supplemental oxygen and intravenous fluids when indicated. • Consider dexamethasone[c] (or equivalent) 8 mg oral or IV. • Consider tocilizumab (or equivalent). When resuming the next planned dose, monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours in an appropriate healthcare setting[b].
Grade 3	Severe symptoms defined as temperature ≥ 100.4°F with: • Hemodynamic instability requiring a vasopressor (with or without	Withhold IMDELLTRA until the event resolves, then resume IMDELLTRA at the next scheduled dose[b].	In addition to Grade 2 treatment: • Recommend intensive monitoring, e.g., ICU care. • Administer dexamethasone[c] (or equivalent) 8 mg IV every 8 hours up to 3 doses. • Vasopressor support as needed. • High flow oxygen support as needed. • Recommend tocilizumab (or equivalent).

CRS Grade	Defining Symptoms	IMDELLTRA Dosage Modification	Management
	vasopressin) and/or • Worsening hypoxia or respiratory distress requiring high flow nasal cannula (> 6 L/min oxygen) or face mask.	For recurrent Grade 3 events, permanently discontinue IMDELLTRA.	Prior to the next dose, administer concomitant medications as recommended for Cycle 1 Day 1 and Cycle 1 Day 8 (see Table 3). When resuming the next planned dose, monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours in an appropriate healthcare setting[b].
Grade 4	Life-threatening symptoms defined as temperature ≥ 100.4°F with: • Hemodynamic instability requiring multiple vasopressors (excluding vasopressin). and/or Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure.	Permanently discontinue IMDELLTRA.	• ICU care. • Per Grade 3 treatment. Recommend tocilizumab (or equivalent)

[a] CRS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).
[b] See Table 4 for recommendations on restarting IMDELLTRA after dose delays *[see Dosage and Administration (2.4)]*.
[c] Taper steroids per standard of care guidelines.

Neurologic Toxicity including ICANS

At the first sign of neurologic toxicity, including ICANS, withhold IMDELLTRA and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care, for severe or life-threatening neurologic toxicities, including ICANS *[see Warnings and Precautions (5.2)]*. Manage ICANS and neurologic toxicity according to the recommendations in Table 6 and consider further management per current practice guidelines.

Table 6. Guidelines for Management of Neurologic Toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)[a]

ICANS Grade[a]	Defining Symptoms	IMDELLTRA Dosage Modifications	Management
Grade 1	ICE score 7-9[b] with no depressed level of consciousness.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c].	• Supportive care.
Grade 2	ICE score 3-6[b] and/or mild somnolence awaking to voice.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c].	• Supportive care. • Dexamethasone[d] (or equivalent) 8 to 10 mg oral or IV. Can repeat every 12 hours or methylprednisolone[d] (or equivalent) 1 mg/kg IV every 12 hours if symptoms worsen. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. • Monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours following the next dose of IMDELLTRA.

ICANS Grade[a]	Defining Symptoms	IMDELLTRA Dosage Modifications	Management
Grade 3	ICE score 0-2[b] and/or depressed level of consciousness awakening only to tactile stimulus and/or any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention and/or Focal or local edema on neuroimaging.	• Withhold IMDELLTRA until the ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c]. • If there is no improvement to Grade ≤ 1 within 7 days permanently discontinue IMDELLTRA. • For recurrent Grade 3 events, permanently discontinue IMDELLTRA.	• Recommend intensive monitoring, e.g., ICU care. • Consider mechanical ventilation for airway protection. • Dexamethasone[d] (or equivalent) 10 mg IV every 6 hours or methylprednisolone[d] (or equivalent) 1 mg/kg IV every 12 hours. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity. Monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours following the next dose of IMDELLTRA.
Grade 4	ICE score 0[b] (patient is unarousable and unable to perform ICE) and/or Stupor or coma and/or Life-threatening prolonged seizure (> 5 minutes) or repetitive clinical or electrical	• Permanently discontinue IMDELLTRA.	• ICU care. • Consider mechanical ventilation for airway protection. • High dose corticosteroids (e.g., methylprednisolone[d] 1000 mg/day in divided doses IV for 3 days). • Consider repeat neuroimaging (CT or MRI) every 2-3

ICANS Grade[a]	Defining Symptoms	IMDELLTRA Dosage Modifications	Management
	seizures without return to baseline in between and/or diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilledema, cranial nerve VI palsy, or Cushing's triad.		days if patient has persistent Grade ≥ 3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.

a. ICANS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019)
b. If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (names 3 objects, e.g., point to clock, pen, button = 3 points); Following commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points
c. See Table 4 for recommendations on restarting IMDELLTRA after dose delays *[see Dosage and Administration (2.4)]*
d. Taper steroids per standard of care guidelines

Table 7. Recommended Treatment Interruptions of IMDELLTRA for the Management of Cytopenias, Infections, and Other Adverse Reactions

Adverse Reactions	Severity[b]	Dosage Modification[a]
Cytopenias *[see Warnings and Precautions (5.3)]*	Grade 3 Neutropenia	Withhold IMDELLTRA until recovery to Grade ≤ 2. Consider administration of granulocyte colony stimulating factor (G-CSF). Permanently discontinue if recovery to Grade ≤ 2 does not occur within 3 weeks.

Adverse Reactions	Severity[b]	Dosage Modification[a]
	Grade 4 Neutropenia	Withhold IMDELLTRA until recovery to Grade ≤ 2. Consider administration of granulocyte colony stimulating factor (G-CSF). Permanently discontinue if recovery to Grade ≤ 2 does not occur within 1 week.
	Recurrent Grade 4 Neutropenia	Permanently discontinue IMDELLTRA
	Febrile neutropenia	Withhold IMDELLTRA until neutropenia recovers to Grade ≤ 2 and fever resolves.
	Hemoglobin <8 g/dL	Withhold IMDELLTRA until hemoglobin is ≥8 g/dL.
	Grade 3 or Grade 4 Decreased platelet count	Withhold IMDELLTRA until platelet count is Grade ≤ 2 and no evidence of bleeding. Permanently discontinue if recovery to Grade ≤ 2 does not occur within 3 weeks.
	Recurrent Grade 4 Decreased platelet count	Permanently discontinue IMDELLTRA.
Infections *[see Warnings and Precautions (5.4)]*	All Grades	Withhold IMDELLTRA in the step-up phase in patients until infection resolves.
	Grade 3	Withhold IMDELLTRA during the treatment phase until infection improves to Grade ≤ 1[a].
	Grade 4	Permanently discontinue IMDELLTRA.
Hepatotoxicity *[see Warnings and Precautions (5.5)]*	Grade 3 Increased ALT or AST or bilirubin	Withhold IMDELLTRA until improved to Grade ≤ 1.
	Grade 4 Increased ALT or AST or bilirubin	Permanently discontinue IMDELLTRA.
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	Permanently discontinue IMDELLTRA.

Adverse Reactions	Severity[b]	Dosage Modification[a]
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or 4	Withhold IMDELLTRA until recovery to Grade ≤ 1 or baseline. Consider permanently discontinuing if adverse reaction does not resolve within 28 days. Consider permanent discontinuation for Grade 4 events.

[a] Refer to Table 4 for dose restarting guidance.
[b] Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

2.6 Preparation

Material Compatibility Information

- IV bags composed of ethyl vinyl acetate (EVA), polyolefin, and polyvinyl chloride (PVC) have been shown to be compatible with IMDELLTRA at the specified administration conditions.
- IV line and catheter materials composed of polyolefin, PVC, and polyurethane have been shown to be compatible with IMDELLTRA at the specified administration conditions.
- The use of Closed System Transfer Device (CSTD) is not recommended due to potential wrong dose medication error risk. Amgen has not performed compatibility testing of vial adaptor CSTDs with IMDELLTRA.

Step 1: Reconstitute IMDELLTRA with Sterile Water for Injection

- Table 8 provides the required amount of sterile water for injection required to reconstitute IMDELLTRA 1 mg and 10 mg vials.

Do not use IV Solution Stabilizer (IVSS) to reconstitute IMDELLTRA.

The IV Solution Stabilizer (IVSS) is used to coat the intravenous bag prior to addition of reconstituted IMDELLTRA to prevent adsorption of IMDELLTRA to IV bags and IV tubing.

Table 8. Required Amount of Sterile Water for Injection to Reconstitute IMDELLTRA[a]

IMDELLTRA Vial Strength	Amount of Sterile Water for Injection Needed to Reconstitute IMDELLTRA	Resulting Concentration
1 mg	1.3 mL	0.9 mg/mL
10 mg	4.4 mL	2.4 mg/mL

[a.] Each vial contains overfill to allow for withdrawal of 1.1 mL (1 mg vial) or 4.2 mL (10 mg vial) after reconstitution to ensure delivery at the stated concentration of labeled vial strength.

- Using a needle and syringe filled with the required amount of sterile water, inject the sterile water against the glass vial. Avoid injecting the water directly onto the powder to prevent foaming.
- Gently swirl the contents to mix. Do not shake.
- Inspect parenteral drug products for particulate matter and discoloration prior to administration. Inspect that the solution is clear to opalescent, colorless to slightly yellow. Do not use if the solution is cloudy or has particulates.
- Further dilute reconstituted IMDELLTRA.
- The reconstituted IMDELLTRA must be further diluted within 4 hours of reconstitution or discarded.

Prepare the infusion bag: Steps 2 to 5

Step 2: Withdraw 0.9% Sodium Chloride for Injection

- Using a 250 mL prefilled bag of 0.9% Sodium Chloride for Injection, withdraw the amount of sodium chloride specified in Table 9 and discard.

Table 9. Required Amount of 0.9% Sodium Chloride to Withdraw from 250 mL IV Bag

IMDELLTRA Vial Strength	IMDELLTRA Dose	Volume of 0.9% Sodium Chloride to Withdraw From 250 mL IV Bag
1 mg	1 mg	14 mL
10 mg	10 mg	17 mL

Step 3: Add IV Solution Stabilizer to the infusion bag

- Inject 13 mL of IV Solution Stabilizer (IVSS) into the 250 mL 0.9% Sodium Chloride infusion bag, see Table 10.
- Gently mix the contents of the infusion bag to avoid foaming. Do not shake.

Table 10. Required Amount of IV Solution Stabilizer (IVSS) to Add to IV Bag

IMDELLTRA Vial Strength	IMDELLTRA Dose	Volume of IV Solution Stabilizer (IVSS) to Add to IV Bag
1 mg	1 mg	13 mL
10 mg	10 mg	13 mL

Step 4: Dilute the reconstituted IMDELLTRA into the infusion bag

- Transfer the required volume of reconstituted IMDELLTRA listed in Table 11 to the infusion bag *(containing IV Solution Stabilizer)*.

NOTE: The final concentrations for the different strength vials are NOT the same following reconstitution and further dilution.

Table 11. Required Amount of Reconstituted IMDELLTRA to Add to 250 mL IV Bag

IMDELLTRA Vial Strength	IMDELLTRA Dose	Volume of Reconstituted IMDELLTRA to Add to 250 mL IV Bag
1 mg	1 mg	1.1 mL
10 mg	10 mg	4.2 mL

- Gently mix the contents of the bag. Do not shake.

Step 5: Remove air from IV bag

Remove air from the prepared IV bag using an empty syringe to avoid foaming.

Step 6: Prime IV tubing

- Prime intravenous tubing with either 0.9% Sodium Chloride for Injection or with the final prepared product.
- See Table 12 for maximum storage time of prepared IMDELLTRA infusion.

Prepared IMDELLTRA Infusion Bag Storage Requirements

- Administer reconstituted and diluted IMDELLTRA immediately.
- Table 12 displays the maximum storage time for the prepared IMDELLTRA infusion bag.
- Maximum storage time includes total duration from the time of reconstitution of the vial of IMDELLTRA to the end of the infusion.

Table 12. Maximum Storage Time for Prepared IMDELLTRA Infusion Bag

	Room Temperature 20°C to 25°C (68°F to 77°F)	Refrigerated 2°C to 8°C (36°F to 46°F)
Prepared IMDELLTRA Infusion Bag	8 hours	7 days

- Discard the prepared IMDELLTRA infusion bag after maximum storage time (from time of reconstitution).
- If refrigerated, allow the prepared IMDELLTRA infusion bag to come room temperature prior to administration, and complete the infusion within 8 hours (including preparation and infusion time).
- Do not re-refrigerate prepared infusion bag.

3 DOSAGE FORMS AND STRENGTHS

For injection: 1 mg of white to slightly yellow lyophilized powder in a single-dose vial for reconstitution and further dilution.

For injection: 10 mg of white to slightly yellow lyophilized powder in a single-dose vial for reconstitution and further dilution.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in 11 Description section.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

IMDELLTRA can cause cytokine release syndrome (CRS) including life-threatening or fatal reactions.

In the pooled safety population *[see Adverse Reactions (6.1)]*, CRS occurred in 57% (268/473) of patients who received IMDELLTRA, including 39% Grade 1, 15% Grade 2, 1.7% Grade 3 and 0.2% Grade 4. Recurrent CRS occurred in 24% of IMDELLTRA-treated patients including 20% Grade 1 and 3.4% Grade 2; one patient experienced recurrent Grade 3.

Among the 268 patients who experienced CRS, 73% had CRS after the first dose, 60% had CRS after the second dose, and 15% had CRS following the third or later dose. Following the Cycle 1 Day 1, Day 8, Day 15 infusions, 24%, 8%, and 1% of patients experienced Grade ≥ 2 CRS, respectively. From Cycle 2 onwards, 1.5% of patients experienced Grade ≥ 2 CRS. Of the patients who experienced CRS, 31% received steroids and 10% required tocilizumab. The median time to onset of all grade CRS from most recent dose of IMDELLTRA was 16 hours (range: start of infusion to 15 days). The median time to onset of Grade ≥ 2 CRS from most recent dose of IMDELLTRA was 15 hours (range: start of infusion to 15 days).

Clinical signs and symptoms of CRS included pyrexia, hypotension, fatigue, tachycardia, headache, hypoxia, nausea and vomiting. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

Administer IMDELLTRA following the recommended step-up dosing and administer concomitant medications before and after Cycle 1 Day 1 and Cycle 1 Day 8 IMDELLTRA infusions as described in Table 3 to reduce the risk of CRS *[see Dosage and Administration (2.3)]*. Administer IMDELLTRA in an appropriate healthcare facility equipped to monitor and manage CRS. Ensure patients are well hydrated prior to administration of IMDELLTRA.

Closely monitor patients for signs and symptoms of CRS during treatment with IMDELLTRA. At the first sign of CRS, immediately discontinue IMDELLTRA infusion, evaluate the patient for hospitalization and institute supportive care based on severity. Withhold or permanently discontinue IMDELLTRA based on severity *[see Dosage and Administration (2.5)]*. Counsel patients and caregivers to seek medical attention should signs or symptoms of CRS occur.

5.2 Neurologic Toxicity Including ICANS

IMDELLTRA can cause life-threatening or fatal neurologic toxicity including ICANS.

In the pooled safety population *[see Adverse Reactions (6.1)]*, neurologic toxicity occurred in 65% of patients who received IMDELLTRA, with Grade 3 or higher events in 7% of patients including fatal events in 0.2%. The most frequent neurologic toxicities were dysgeusia (34%), headache (17%), peripheral neuropathy (9%), dizziness (9%), and insomnia (8%).

The incidence of signs and symptoms consistent with ICANS was 10% in IMDELLTRA-treated patients, including events with the preferred terms: ICANs (4.7%), muscular weakness (3.2%), cognitive disorder (0.6%), aphasia (0.6%), depressed level of consciousness (0.4%), seizures (0.4%), encephalopathy (0.4%), and leukoencephalopathy (0.2%). There was one fatal reaction of ICANS *[see Adverse Reactions (6.1)]*. Recurrent ICANS occurred in 1.5% of patients. Of the patients who experienced ICANS, most experienced the event following Cycle 1 Day 1 (2.5%) and Cycle 1 Day 8 (3.6%). Following Day 1, Day 8, and Day 15 infusions, 1.3%, 1.3% and 0.4% of patients experienced Grade ≥ 2 ICANS, respectively. ICANS can occur several weeks following administration of IMDELLTRA. The median time to onset of ICANS from the first dose of IMDELLTRA was 16 days (range: 1 to 862 days). The median time to resolution of ICANS was 4 days (range: 1 to 40 days).

The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical signs and symptoms of ICANS may include but are not limited to confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia.

Patients receiving IMDELLTRA are at risk of neurologic adverse reactions and ICANS resulting in depressed level of consciousness. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until neurologic symptoms resolve.

Closely monitor patients for signs and symptoms of neurologic toxicity and ICANS during treatment with IMDELLTRA. At the first sign of ICANS, immediately discontinue the infusion, evaluate the patient and provide supportive therapy based on severity. Withhold IMDELLTRA or permanently discontinue based on severity *[see Dosage and Administration (2.5)]*.

5.3 Cytopenias

IMDELLTRA can cause cytopenias including neutropenia, thrombocytopenia, and anemia.

In the pooled safety population, *[see Adverse Reactions (6.1)]* based on laboratory data, decreased neutrophils occurred in 16% of patients, including 9% Grade 3 or 4. The median time to onset for Grade 3 or 4 decreased neutrophil count was 41 days (range: 2 to 306 days). Decreased platelets occurred in 30%, including 2.2% Grade 3 or 4. The median time to onset for Grade 3 or 4 decreased platelets was 67 days (range: 3 to 420 days). Decreased hemoglobin occurred in 56% of patients, including 4.7% Grade 3 or 4.

Febrile neutropenia was reported as an adverse event in 1.5% of patients treated with IMDELLTRA.

Monitor patients for signs and symptoms of cytopenias. Perform complete blood counts prior to treatment with all doses of IMDELLTRA, up through Cycle 5 Day 15 and then prior to administration of IMDELLTRA on Day 1 of each cycle starting with Cycle 6. Based on the severity of cytopenias, temporarily withhold or permanently discontinue IMDELLTRA *[see Dosage and Administration (2.5)]*.

5.4 Infections

IMDELLTRA can cause serious infections, including life-threatening and fatal infections.

In the pooled safety population, *[see Adverse Reactions (6.1)]*, infections including opportunistic infections occurred in 43% of patients who received IMDELLTRA, including 14% Grade 3 or 4. The most frequent infections were pneumonia (11%), urinary tract infection (9%), COVID-19 (6%), upper respiratory tract infection (4.7%), respiratory tract infection (4%), candida infection (2.1%), oral candidiasis (2.1%) and nasopharyngitis (2.1%).

Monitor patients for signs and symptoms of infection prior to and during treatment with IMDELLTRA and treat as clinically indicated. Withhold or permanently discontinue IMDELLTRA based on severity *[see Dosage and Administration (2.5)]*.

5.5 Hepatotoxicity

IMDELLTRA can cause hepatotoxicity.

In the pooled safety population *[see Adverse Reactions (6.1)]*, based on laboratory data, elevated ALT occurred in 39% of patients who received IMDELLTRA, including 2.5% Grade 3 or 4 ALT. Elevated AST occurred in 43% of patients, including 3.2% Grade 3 or 4. Elevated bilirubin occurred in 16% of patients, including 1.3% Grade 3 or 4 *[see Adverse Reactions (6.1)]*. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin prior to treatment with IMDELLTRA, and as clinically indicated. Withhold IMDELLTRA or permanently discontinue based on severity *[see Dosage and Administration (2.5)]*.

5.6 Hypersensitivity

IMDELLTRA can cause severe hypersensitivity reactions.

Clinical signs and symptoms of hypersensitivity may include, but are not limited to, rash and bronchospasm.

Monitor patients for signs and symptoms of hypersensitivity during treatment with IMDELLTRA and manage as clinically indicated. Withhold or consider permanent discontinuation of IMDELLTRA based on severity *[see Dosage and Administration (2.5)]*.

5.7 Embryo-Fetal Toxicity

Based on its mechanism of action, IMDELLTRA may cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMDELLTRA and for 2 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome (CRS) *[see Warnings and Precautions (5.1)]*
- Neurologic Toxicity Including ICANS *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Infections *[see Warnings and Precautions (5.4)]*
- Hepatotoxicity *[see Warnings and Precautions (5.5)]*
- Hypersensitivity *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to intravenous IMDELLTRA, as a single agent, at the recommended dosage of IMDELLTRA 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 in 473 patients with small cell lung cancer enrolled in three clinical trials: DeLLphi-300, DeLLphi-301 and DeLLphi-304. Among 473 patients who received IMDELLTRA, 40% were exposed for 6 months or longer and 19% were exposed for greater than one year. The most common (≥ 20%) adverse reactions were CRS (57%), fatigue (48%), decreased appetite (38%), dysgeusia (34%), pyrexia (33%), constipation (31%), musculoskeletal pain (31%), and nausea (25%). The most common (≥ 5%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes (43%), decreased sodium (12%), decreased total neutrophils (9%), and increased uric acid (6%).

Extensive Stage Small Cell Lung Cancer

The safety of IMDELLTRA was evaluated in 252 patients in DeLLphi-304, a multicenter, randomized, open label trial in patients with extensive stage small cell lung cancer (ES-

SCLC) with disease progression following treatment with platinum-based chemotherapy with or without an anti-PD-(L)1 antibody *[see Clinical Studies (14.1)].* Patients received IMDELLTRA (n=252) or investigator's choice or investigator's choice of topotecan [n=176], lurbinectedin [n=45] or amrubicin [n=23].

Among patients who received IMDELLTRA, 41% were exposed for 6 months or longer and 18% were exposed for greater than one year.

The demographic characteristics of patients who received IMDELLTRA were: median age 64 years (range: 20 to 86); 71% male; 60% White, 38 % Asian, 0.8% Black or African American; and 4.8% were of Hispanic or Latino ethnicity.

Serious adverse reactions occurred in 52% of patients who received IMDELLTRA. Serious adverse reactions in >3% of patients included CRS (17%), pyrexia (6%), pneumonia (5%) and ICANS (3.6%). Fatal adverse reactions occurred in 8% of patients who received IMDELLTRA, including one fatal adverse reaction of ICANS (0.4%). Fatal adverse reactions occurring in more than one patient included pneumonia (1.6%), cardio-respiratory arrest (1.6%), and sepsis (0.8%).

Permanent discontinuation of IMDELLTRA due to an adverse reaction occurred in 6% of patients. Adverse reactions which resulted in permanent discontinuation of IMDELLTRA in > 1% of patients included pneumonia (1.2%).

Dosage interruptions of IMDELLTRA due to an adverse reaction occurred in 38% of patients. Adverse reactions which required dosage interruption in ≥ 2% of patients included neutropenia (5%), fatigue (4.4%), pneumonia (4%), decreased appetite (2.8%), COVID-19 (2%).

Table 13 summarizes adverse reactions observed in DeLLphi-304.

Table 13. Adverse Reactions (≥ 15%) in Patients with SCLC Who Received IMDELLTRA in DeLLphi-304

Adverse Reaction	IMDELLTRA[a] (N = 252)		Standard of Care (N = 244)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Immune system disorders				
Cytokine release syndrome[b]	56	1.2	1.2	0
General disorders and administration site conditions				
Fatigue[c]	39	6	43	10
Pyrexia[d]	29	1.2	11	1.2
Metabolism and nutrition disorders				
Decreased appetite	37	2	23	1.6
Gastrointestinal disorders				

Adverse Reaction	IMDELLTRA[a] (N = 252)		Standard of Care (N = 244)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Constipation	30	0.4	22	0
Nausea	25	0.4	32	0
Nervous system disorders				
Dysgeusia[e]	28	0	2.5	0
Headache[f]	16	0	9	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[g]	27	1.6	21	2.5
Respiratory, thoracic and mediastinal disorders				
Cough[h]	17	0	17	0

[a] Graded using CTCAE Version 4.0 and Version 5.0.
[b] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019.
[c] Includes fatigue and asthenia
[d] Includes body temperature increased, hyperthermia, pyrexia
[e] Includes ageusia, dysgeusia, hypogeusia
[f] Includes headache and tension headache
[g] Includes arthralgia, back pain, bone pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
[h] Includes cough and productive cough

Clinically relevant adverse reactions occurring in < 15% of patients who received IMDELLTRA were immune effector cell-associated neurotoxicity syndrome, neurotoxicity, tremor, seizure, ataxia, confusional state, delirium, dyspnea, encephalopathy and weight decreased.

Table 14 summarizes laboratory abnormalities in DeLLphi-304.

Table 14. Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with SCLC in DeLLphi-304

Laboratory Abnormality	IMDELLTRA[a] N=252		Standard of care N=244	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Lymphocytes decreased	65	27	62	27
Hemoglobin decreased	51	4.5	86	29
White blood cells decreased	50	7	70	29

Laboratory Abnormality	IMDELLTRA[a] N=252		Standard of care N=244	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Platelets decreased	25	0.4	55	20
Neutrophils decreased[b]	15	10	44	36
Chemistry				
Sodium decreased	57	8	38	7
Potassium decreased	41	4.8	34	4
Aspartate amino transferase increased	40	2.8	29	0.4
Sodium increased	35	0.4	27	0
Alanine aminotransferase increased	32	2	25	0.9
Activated Partial Thromboplastin Time (sec) increased	26	1.3	16	0.9
Creatinine increased	23	0.8	19	0.4
Alkaline phosphate increased	22	0.4	26	1.4
Magnesium decreased	21	0.8	15	1.8
Potassium increased	21	0.8	12	1.8
Creatine Phosphokinase increased	21	1.7	11	0

[a] The denominator used to calculate the rate varied for IMDELLTRA (Range: 229 to 250) and SOC (Range: 205 to 226) based on the number of patients with a baseline value and at least one post-treatment value.
[b] All Grade lab abnormalities occurring at a frequency less than 20% included decreased neutrophils.

DeLLphi-300 and DeLLphi-301

The safety of IMDELLTRA, as a single agent, at the recommended dosage was evaluated in patients with extensive stage small cell lung cancer enrolled in DeLLphi-300 and DeLLphi-301 *[see Clinical Studies (14.1)].* Among 187 patients who received IMDELLTRA, 31% were exposed for 6 months or longer and 14% were exposed for greater than one year.

The demographic characteristics of patients who received IMDELLTRA were: median age 66 years (range: 35 to 82); 65% male; 70% White, 26% Asian, 2.1% Black or African American; and 2.1% Hispanic or Latino.

Serious adverse reactions occurred in 58% of patients who received IMDELLTRA. Serious adverse reactions in >3% of patients included cytokine release syndrome

(24%), pneumonia (6%), pyrexia (3.7%) and hyponatremia (3.6%). Fatal adverse reactions occurred in 2.7% of patients who received IMDELLTRA including pneumonia 0.5%, aspiration (0.5%), pulmonary embolism (0.5%), respiratory acidosis (0.5%), and respiratory failure (0.5%).

Permanent discontinuation of IMDELLTRA due to an adverse reaction occurred in 7% of patients. Adverse reactions which resulted in permanent discontinuation of IMDELLTRA in >1% of patients included cytokine release syndrome (1.6%) and tumor lysis syndrome (1.1%).

Dosage interruptions of IMDELLTRA due to an adverse reaction occurred in 27% of patients. Adverse reactions which required dosage interruption in ≥ 2% of patients included fatigue (3.2%), cytokine release syndrome (2 .7%) and respiratory tract infection (2.1%).

Table 15 summarizes adverse reactions observed in DeLLphi-300 and DeLLphi-301.

Table 15. Adverse Reactions (≥ 15%) in Patients with ES-SCLC Who Received IMDELLTRA in DeLLphi-300 and DeLLphi-301

Adverse Reaction	**IMDELLTRA* (N = 187)**	
	Any Grade (%)	**Grade 3 or 4 (%)**
Immune system disorders		
Cytokine release syndrome†	55	1.6
General disorders and administration site conditions		
Fatigue‡	51	10
Pyrexia	36	0
Nervous system disorders		
Dysgeusia	36	0
Metabolism and nutrition disorders		
Decreased appetite	34	2.7
Nausea	22	1.6
Gastrointestinal disorders		
Constipation	30	0.5
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain§	30	1.1

Respiratory, thoracic and mediastinal disorders		
Dyspnea¶	17	2.1
Cough	17	0

*Graded using CTCAE Version 4.0 and Version 5.0.
†Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019.
‡Includes fatigue and asthenia.
§Includes myalgia, arthralgia, back pain, pain in extremity, neck pain, musculoskeletal chest pain, non-cardiac chest pain and bone pain.
¶Includes dyspnea and exertional dyspnea.

Table 16 summarizes laboratory abnormalities in DeLLphi-300 and DeLLphi-301.

Table 16. Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with ES - SCLC in DeLLphi-300 and DeLLphi-301

	IMDELLTRA*	
	All Grades (%)	**Grade 3 or 4 (%)**
Laboratory Abnormality		
Hematology		
Lymphocytes decreased	84	57
Hemoglobin decreased	58	5
White blood cells decreased	44	3.8
Platelets decreased	33	3.2
Neutrophils decreased†	12	6
Chemistry		
Sodium decreased	68	16
Potassium decreased	50	5
Aspartate amino transferase increased	44	3.2
Alanine aminotransferase increased	42	2.1
Magnesium decreased	33	1.6
Creatinine increased	29	0.5
Sodium increased	26	0
Alkaline phosphate increased	22	0

*The denominator used to calculate the rate varied from 41 to 187 based on the number of patients with a baseline value and at least one post-treatment value.

†All Grade lab abnormalities occurring at a frequency less than 20% included decreased neutrophils.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, IMDELLTRA may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of IMDELLTRA in pregnant women to inform a drug-associated risk.

In an animal reproduction study, a murine surrogate molecule administered intravenously to pregnant mice crossed the placental barrier.

Tarlatamab causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance.

Human immunoglobulin G (IgG) and proteins comprising IgG-derived fragment crystallizable (Fc) domains are known to cross the placental barrier; therefore, IMDELLTRA has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with tarlatamab. In an embryo-fetal developmental toxicity study, a murine surrogate molecule was administered intravenously to pregnant mice during the period of organogenesis. The surrogate molecule crossed the placental barrier and did not cause maternal toxicity, embryo-fetal toxicity or teratogenicity.

8.2 Lactation

Risk Summary

There are no data on the presence of tarlatamab in human milk or the effects on the breastfed child or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to IMDELLTRA are unknown. Because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with IMDELLTRA and for 2 months after the last dose.

8.3 Females and Males of Reproductive Potential

IMDELLTRA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating IMDELLTRA.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with IMDELLTRA and for 2 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of IMDELLTRA have not been established in pediatric patients.

8.5 Geriatric Use

Of the 473 patients with SCLC who received IMDELLTRA 10 mg as a single agent, 51% were 65 years of age or older and 11% were 75 years of age or older. No overall differences in IMDELLTRA pharmacokinetics, safety or efficacy were observed between older patients (≥ 65 years of age) and younger patients.

10 OVERDOSAGE

There is no clinical experience with overdose with IMDELLTRA. Doses up to 100 mg every two weeks and 200 mg every three weeks have been administered in clinical trials. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

11 DESCRIPTION

Tarlatamab is a bispecific DLL3-directed CD3 T-cell engager that binds to DLL3 expressed on the surface of cells, including tumor cells, and CD3 expressed on the surface of T cells. Tarlatamab is produced using recombinant DNA technology in Chinese hamster ovary cells. It consists of 982 amino acids and has a molecular weight of approximately 105 kilodaltons.

IMDELLTRA (tarlatamab) for injection is supplied as a sterile, preservative-free, white to slightly yellow, lyophilized powder in a single-dose vial for reconstitution and further dilution.

Each 1 mg vial contains tarlatamab (1 mg), glutamic acid (0.72 mg), polysorbate 80 (0.04 mg), sucrose (37.1 mg), and sodium hydroxide to adjust pH to 4.2. After reconstitution with 1.3 mL of Sterile Water for Injection the resulting concentration is 0.9 mg/mL IMDELLTRA.

Each 10 mg vial contains tarlatamab (10 mg), glutamic acid (3.7 mg), polysorbate 80 (0.2 mg), sucrose (194.4 mg), and sodium hydroxide to adjust pH to 4.2. After reconstitution with 4.4 mL of Sterile Water for Injection the resulting concentration is 2.4 mg/mL IMDELLTRA.

IV Solution Stabilizer is supplied as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each vial of IV Solution Stabilizer contains citric acid monohydrate (36.75 mg), lysine hydrochloride (1598.8 mg), polysorbate 80 (7 mg), sodium hydroxide to adjust pH to 7.0, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tarlatamab is a bispecific T-cell engager that binds to DLL3 expressed on the surface of cells, including tumor cells, and CD3 expressed on the surface of T cells. Tarlatamab causes T-cell activation, release of inflammatory cytokines, and lysis of DLL3-expressing cells. Tarlatamab had anti-tumor activity in mouse models of SCLC.

12.2 Pharmacodynamics

Exposure-Response Relationships

There are no clinically significant exposure-response relationships for efficacy over the exposure range observed between tarlatamab 10 mg and 100 mg (10 times the highest approved recommended dosage).

There is an exposure-response relationship between tarlatamab exposure and neutropenia or neurologic toxicity including ICANS with a higher risk of any grade neutropenia or neurologic toxicity including ICANS at higher exposure.

Serum Cytokines

Transient elevation of serum cytokines IL-2, IL-6, IL-8, IL-10, and IFN-γ were observed at a tarlatamab dosage of 0.3 mg and above. Peak elevation of cytokines was generally observed 24 hours following the initial dose of IMDELLTRA at 1 mg on Cycle 1 Day 1 and generally returned to baseline levels prior to the next infusion on Cycle 1 Day 8.

12.3 Pharmacokinetics

Tarlatamab pharmacokinetic data in patients with SCLC at the approved recommended dosage are presented as mean (CV%) unless otherwise specified. The exposure of tarlatamab-dlle increases in a dose proportional manner over the dosage range of 1 mg to 100 mg (10 times the highest approved recommended dosage) every 2 weeks. Tarlatamab steady state is achieved by Cycle 2 Day 15. Pharmacokinetic parameters are summarized for the recommended dosage of IMDELLTRA in Table 17.

Table 17. Pharmacokinetic Parameters of Tarlatamab

	Parameter		
	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
First step-up dose 1 mg	106 (26%)	314 (35%)	49 (35%)
First treatment dose 10 mg	1,100 (26%)	3,190 (35%)	517 (36%)

	Parameter		
	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
Steady state 10 mg every 2 weeks	1,040 (37%)	3,640 (35%)	472 (62%)

Distribution

Tarlatamab steady state volume of distribution is 8.5 L (33%).

Metabolism

Tarlatamab is expected to be metabolized into small peptides by catabolic pathways.

Elimination

Tarlatamab terminal elimination half-life is 11 days (31%) with an estimated systemic clearance of 0.7 L/day (34%).

Specific Populations

No clinically significant differences in the pharmacokinetics of tarlatamab were observed based on age (20 to 86 years), body weight (35 to 149 kg), sex, race (68% White and 27% Asian), mild or moderate renal impairment (eGFR 30 to < 90 mL/min), or mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN).

The effects of severe renal impairment (eGFR 15 to < 30 mL/min), end-stage renal disease (eGFR <15 mL/min), or moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and any AST) on the pharmacokinetics of tarlatamab are unknown.

Effects of Tarlatamab on CYP450 Substrates

Tarlatamab causes transient release of cytokines that may suppress CYP450 enzymes and may result in an increased exposure of concomitant CYP substrates during and up to 14 days after occurrence of cytokine release syndrome *[see Clinical Pharmacology (12.2)]*.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of tarlatamab or of other tarlatamab products.

During the maximum 3-year treatment period during which the presence of ADA was evaluated in DeLLphi-300, DeLLphi-301, and DeLLphi-304, 8% (36/445) of patients who received the recommended step-up and full dose of IMDELLTRA developed treatment-emergent ADA. In DeLLphi-301 and DeLLphi-304, which included neutralizing antibody assessments, 38% (11/29) of the patients who developed treatment-emergent ADA also developed neutralizing antibodies. ADA resulted in a 14% increase in the clearance of tarlatamab. Because of the low occurrence of ADA, the effect of these antibodies on the

pharmacokinetics, pharmacodynamics, safety, and effectiveness of tarlatamab is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with tarlatamab.

No studies have been conducted to evaluate the effects of tarlatamab on fertility.

14 CLINICAL STUDIES

14.1 Small Cell Lung Cancer

DeLLphi-304

The efficacy of IMDELLTRA was evaluated in DeLLphi-304 (NCT05740566), a multicenter, randomized, open-label trial. Eligible patients were required to have SCLC with disease progression following treatment with platinum-based chemotherapy with or without an anti-PD-(L)1 antibody. Patients were required to have an ECOG Performance Status of 0 or 1 and at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Patients with symptomatic brain metastases or active immunodeficiency were ineligible.

A total of 509 patients were randomized 1:1 to receive either IMDELLTRA (N=254) at an 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 or Investigator's choice of standard of care (SOC) chemotherapy (N=255) (topotecan [73%], lurbinectedin [18%] or amrubicin [9%]) until unacceptable toxicity or disease progression. Randomization was stratified by prior anti-PD-(L)1 exposure (yes versus no), platinum sensitivity status (chemotherapy-free interval (CFI) ≥ 180 days, < 180 to ≥ 90 days, or < 90 days), presence (previous or current) of brain metastases (yes versus no) and investigator's choice of standard of care (topotecan/amrubicin versus lurbinectedin).

The median age was 65 years (range: 20 to 86); 52% age 65 or older; 69% male; 57% White, 40% Asian**,** 1.4% were other races or had race not reported, 1% Black or African American, 0.4% American Indian or Alaska Native; 32% had ECOG PS of 0 and 67% ECOG PS of 1; 100% had extensive stage disease at baseline of whom 91% had metastatic disease; 45% had brain metastases at baseline; 35% had liver metastases at baseline. Sixty-nine percent (69%) of patients were former smokers, 21% were current smokers, 11% were never smokers. All patients received prior platinum therapy; 71% received prior anti-PD-(L)1 therapy; 223 patients (44%) had chemotherapy-free interval < 90 days after end of first line platinum therapy, while 286 patients (56%) had chemotherapy-free interval ≥ 90 days.

The major efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures included progression-free survival (PFS) based on investigator

assessment per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and select patient reported outcomes.

Efficacy results are summarized in Table 18 and Figure 1.

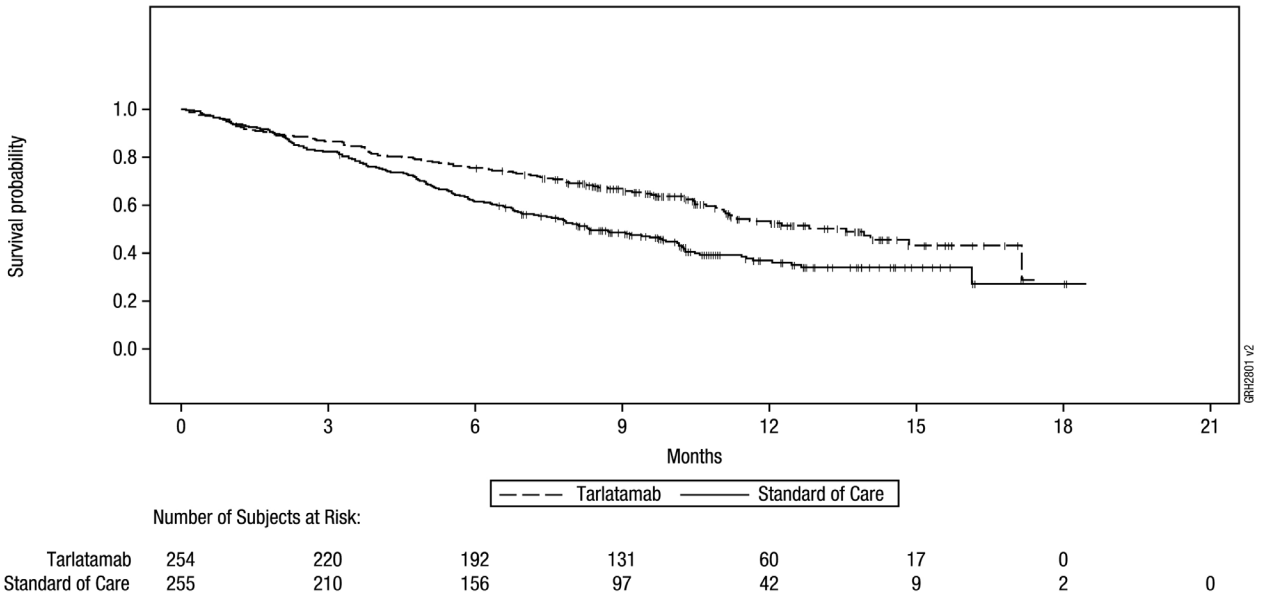
Table 18. Efficacy Results for Patients with SCLC who received IMDELLTRA

Efficacy Parameter	IMDELLTRA (N = 254)	Standard of Care (N = 255)
Overall Survival (OS)		
Deaths (%)	111 (43.7)	152 (59.6)
Median[a] in months (95% CI)	13.6 (11.1, NE)	8.3 (7.0, 10.2)
Hazard ratio[b] (95% CI)	0.60 (0.47, 0.77)	
p-value[c]	<0.001	
Progression-free Survival (PFS)[d]		
Events (%)	191 (75.2)	205 (80.4)
Median[a] in months (95% CI)	4.2 (3.0, 4.4)	3.2 (2.9, 4.2)
Hazard ratio[b] (95% CI)	0.72 (0.59, 0.88)	
p-value[c]	<0.001	

[a] per Kaplan-Meier estimates
[b] Hazard ratio based on the stratified Cox proportional hazard model
[c] p-value based on the stratified log-rank test
[d] PFS based on investigator assessment per RECIST 1.1

In a pre-specified exploratory subgroup analysis, the HR for OS was similar between patients with a chemotherapy-free interval (CFI) <90 days (n=223) and patients with a CFI ≥90 days (n=286), with HRs of 0.60 (95% CI: 0.43, 0.84) and 0.65 (95% CI: 0.45, 0.93), respectively.

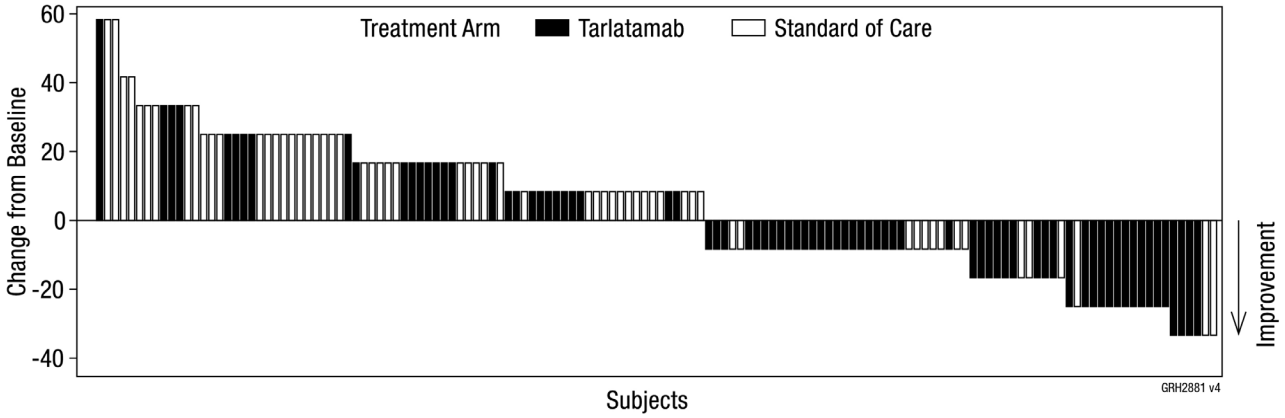
Figure 1: Kaplan-Meier Plot of Overall Survival in ITT on DeLLphi-304



The analysis of mean change from baseline in dyspnea as assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 at week 18 demonstrated a statistically significant improvement in patients randomized to IMDELLTRA compared to SOC. At week 18, 149 patients (59%) randomized to IMDELLTRA and 116 (45%) patients randomized to SOC were still on treatment, and the compliance rates were 79% and 76% respectively at that timepoint.

Figure 2 shows the change from baseline in dyspnea at week 18 in patients who had a change from baseline score at week 18 (n=116 for IMDELLTRA, n=88 for SOC). Two patients with a missing baseline value, both from the IMDELLTRA arm, are not included in the waterfall plot. Patients with no change in dyspnea score are not graphically represented in Figure 2 (n=38 for IMDELLTRA, n=26 for SOC).

Figure 2: Waterfall plot of Change From Baseline in Dyspnea (Composite Score) at Week 18



DeLLphi-301

The efficacy of IMDELLTRA was evaluated in DeLLphi-301 [NCT05060016], an open-label, multicenter, multi-cohort clinical trial. Eligible patients were required to have relapsed/refractory SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy, 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). The trial excluded patients with symptomatic brain metastases, evidence of interstitial lung disease or non-infectious pneumonitis, and active immunodeficiency.

A total of 99 patients received IMDELLTRA intravenously at an 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 study population characteristics were: median age 64 years (range: 35 to 82); 48% of patients ≥ 65 years and 10% of patients ≥ 75 years; 72% male; 58% White, 41% Asian; 1% Hispanic or Latino; and 74% have ECOG 1.

Ninety-seven percent of patients had metastatic disease at baseline; 22% had brain metastases at baseline; and 92% were former/current smokers. All patients received prior platinum-based chemotherapy (median two lines); 74% received prior anti-PD-(L)1 therapy (including 59% who received anti-PD[L]1 therapy in combination with platinum-based chemotherapy in the frontline setting); 51% received prior topoisomerase I inhibitor (including 20% who received topotecan). Platinum sensitivity status, defined by time to progression after first line platinum therapy, was known for 69/99 patients. Twenty-seven patients (27%) had platinum-resistant SCLC, defined as time to progression < 90 days after first line platinum therapy, while 42 patients (42%) had platinum-sensitive SCLC.

Tumor assessments were performed every 6 weeks for the first 48 weeks and every 12 weeks thereafter. The major efficacy outcome measures were overall response rate

(ORR) and duration of response (DOR) as evaluated by Blinded Independent Central Review (BICR) according to RECIST v1.1.

Efficacy results are presented in Table 19.

Table 19. Efficacy Results for DeLLphi-301

Efficacy Parameter	IMDELLTRA (N = 99)
Overall Response Rate (ORR)	
ORR, % (95% CI)[a]	40 (31, 51)
Complete Response, n (%)	2 (2)
Partial Response, n (%)	38 (38)
Duration of Response (DOR)[a]	
Median[b], months (range)	9.7 (2.7, 20.7+)
Duration ≥ 6 months[c], %	68
Duration ≥ 12 months[c], %	40

[a] Assessed by Blinded Independent Central Review, CI = Confidence Interval
[b] Median based on Kaplan-Meier estimate.
[c] Based on observed duration of response.

Of the 69 patients with available data regarding platinum sensitivity status, the ORR was 52% (95% CI: 32, 71) in 27 patients with platinum-resistant SCLC and 31% (95% CI: 18, 47) in 42 patients with platinum-sensitive SCLC.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

IMDELLTRA (tarlatamab) for injection is a sterile, preservative-free, white to slightly yellow, lyophilized powder supplied as follows:

- 1 mg package contains 1 single-dose vial of 1 mg IMDELLTRA and 2 vials of 7 mL IV Solution Stabilizer.
- 10 mg package contains 1 single-dose vial of 10 mg IMDELLTRA and 2 vials of 7 mL IV Solution Stabilizer.

16.2 Storage and Handling

Store IMDELLTRA and IV Solution Stabilizer (IVSS) vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze.

IMDELLTRA and IV Solution Stabilizer (IVSS) vials may be kept at room temperature between 20°C to 25°C (68°F to 77°F) for up to 24 hours in the original carton to protect from light.

17 PATIENT COUNSELING INFORMATION

Cytokine Release Syndrome (CRS)

Inform patients and their caregivers of the risk of CRS, and to immediately contact their healthcare provider for signs and symptoms associated with CRS including pyrexia, hypotension, fatigue, tachycardia, headache, hypoxia, nausea and vomiting *[see Warnings and Precautions (5.1)]*.

Advise patients that they should be monitored from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 doses in an appropriate healthcare setting *[see Warnings and Precautions (5.1)]*.

Advise patients to remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA following Cycle 1 Day 1 and Cycle 1 Day 8 doses, accompanied by a caregiver.

Neurologic Toxicity Including Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

Discuss the signs and symptoms associated with ICANS with patients and their caregivers. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of ICANS, such as encephalopathy, confusion, delirium, seizure, ataxia, weakness or numbness of arms and legs, tremor, and headache.

Advise patients who experience neurologic toxicity or symptoms of ICANS to refrain from driving, operating heavy or potentially dangerous machinery, and engaging in hazardous occupations or activities during treatment with IMDELLTRA *[see Warnings and Precautions (5.2)]*.

Cytopenias

Discuss the signs and symptoms associated with cytopenias, including neutropenia and febrile neutropenia, anemia, and thrombocytopenia with patients and their caregivers *[see Warnings and Precautions (5.3)]*. Inform patients that they will need to undergo lab tests to monitor blood counts. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of cytopenias.

Infections

Discuss the signs and symptoms of infections with patients and their caregivers. Advise patients of the risk of serious infections, and to immediately contact their healthcare provider for signs or symptoms of infections *[see Warnings and Precautions (5.4)]*.

Hepatotoxicity

Discuss the signs and symptoms of hepatotoxicity and bilirubin with patients and their caregivers. Inform patients that they will need to undergo lab tests to monitor liver function. Advise patients to immediately contact their healthcare provider for signs and symptoms of liver dysfunction *[see Warnings and Precautions (5.5)]*.

Hypersensitivity

Discuss the signs and symptoms of allergic reactions with patients and their caregivers. Advise patients to immediately seek medical attention for any signs and symptoms of severe reactions *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider if they are pregnant or become pregnant. Advise females of reproductive potential to use effective contraception during treatment with IMDELLTRA and for 2 months after the last dose *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment with IMDELLTRA and for 2 months after the last dose *[see Use in Specific Populations (8.2)]*.

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Date of revision: December 2025

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