IMDELLTRA™: Cytokine Release Syndrome (CRS) & Neurologic Toxicity/ Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS) Guide

INDICATION

IMDELLTRA™ (tarlatamab-dlle) 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.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

- **Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving IMDELLTRA™. Initiate treatment with IMDELLTRA™ using the step-up dosing schedule to reduce the incidence and severity of CRS. Withhold IMDELLTRA™ until CRS resolves or permanently discontinue based on severity.**
- **Neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), including serious or life-threatening reactions, can occur in patients receiving IMDELLTRA™. Monitor patients for signs and symptoms of neurologic toxicity, including ICANS, during treatment and treat promptly. Withhold IMDELLTRA™ until ICANS resolves or permanently discontinue based on severity.**

Please see additional Important Safety Information, including BOXED WARNINGS, on pages 14–15.

IMDELLTRA™ (tarlatamab-dlle) for injection 1 mg & 10 mg single-use vials

Table of contents

CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome.

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Understanding cytokine release syndrome (CRS)

CRS is an acute systemic inflammatory response to immunotherapy characterized by fever and multiple organ dysfunction.[1] IMDELLTRA™ can cause CRS, including serious or life-threatening reactions.[2]

Signs, symptoms, and potential complications

- **CRS symptoms are progressive, and can include fever at the onset**[3]
- Clinical signs and symptoms of CRS include pyrexia, hypotension, fatigue, tachycardia, headache, hypoxia, nausea, and vomiting[2]
- **Potentially life-threatening complications** may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC)[2]

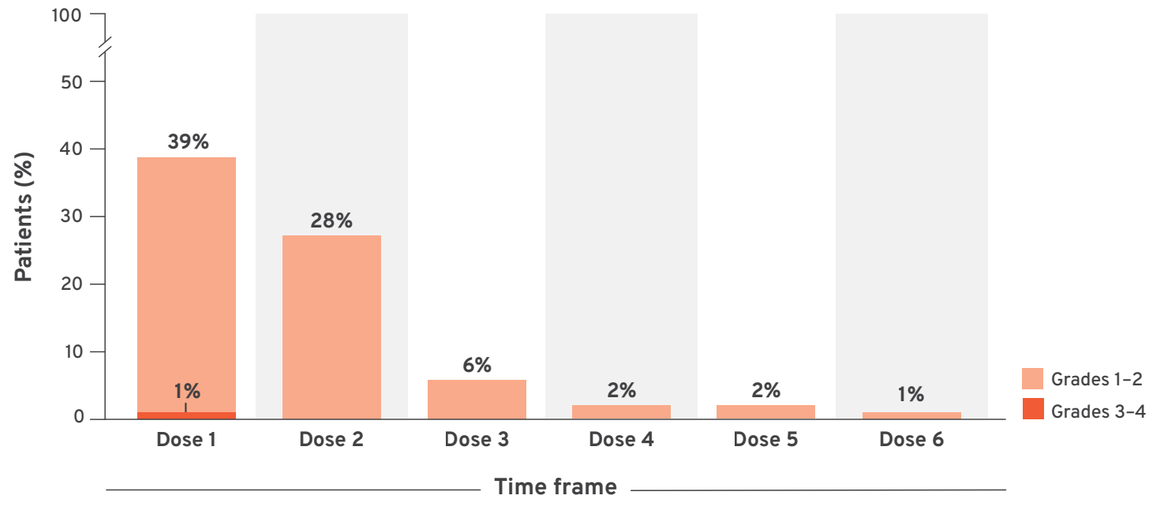
Grading CRS[2]

Grade*	Defining Symptoms
Grade 1	Symptoms require symptomatic treatment only (eg, fever ≥ 100.4°F without hypotension or hypoxia)
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
Grade 3	Severe symptoms defined as temperature ≥ 100.4°F with: • Hemodynamic instability requiring a vasopressor (with or without vasopressin) or • Worsening hypoxia or respiratory distress requiring high-flow nasal cannula (> 6 L/min oxygen) or face mask
Grade 4	Life-threatening symptoms defined as temperature ≥ 100.4°F with: • Hemodynamic instability requiring multiple vasopressors (excluding vasopressin) • Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure

*Based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).[2]

Most CRS events were Grade 1 and occurred following the first two doses of IMDELLTRA™ 2,†

CRS events across treatment doses in the DeLLphi-301 study[4,‡]



In the DeLLphi-300 and DeLLphi-301 pooled safety population, most events (43%) of CRS occurred after the first dose, with 29% of patients experiencing any Grade CRS after the second dose and 9% following the third dose or later. Following the Day 1, Day 8, and Day 15 infusions, 16%, 4.3%, and 2.1% of patients experienced ≥ Grade 2 CRS, respectively.[2,†]

- 55% (n=103/187) of patients who received IMDELLTRA™ experienced any Grade CRS[2,†]
- 34% (n=64/187), 19% (n=36/187), 1.1% (n=2/187), and 0.5% (n=1/187) of patients experienced Grade 1, 2, 3, and 4 CRS, respectively[2,†]
- Recurrent CRS occurred in 24% of patients treated with IMDELLTRA™, including 18% Grade 1 and 6% Grade 2[2,†]
- Nearly all CRS events resolved, and most cases were managed with supportive care, such as acetaminophen, IV hydration, and glucocorticoids[4,‡]
- 6.8% (n=9/133) of patients required IV fluids, 8.3% (n=11/133) required supplemental oxygen, 5.3% (n=7/133) required tocilizumab, and 0.8% (n=1/133) required vasopressor support (excluding vasopressin)[5,‡]

†Based on the pooled safety population of 187 patients enrolled in DeLLphi-300 and DeLLphi-301 who received IMDELLTRA™ 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8, 15, and then Q2W until disease progression or intolerable toxicity.[2]
‡Based on 133 patients who received IMDELLTRA™ 10 mg in the DeLLphi-301 study.[4]

IV, intravenous; Q2W, every 2 weeks.

Please see additional Important Safety Information, including BOXED WARNINGS, on pages 14–15.

Onset and duration of CRS with IMDELLTRA™

Median onset of all Grade CRS from most recent dose of IMDELLTRA™[2,*]

13.5 hours

(1–268 hours)

Median duration[4,†]

4 days

(IQR 2–6)

The median time to onset of Grade ≥ 2 CRS from most recent dose was 14.6 hours (2–566 hours).[2,*]

*Based on the pooled safety population of 187 patients enrolled in DeLLphi-300 and DeLLphi-301 who received IMDELLTRA™ 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8, 15, and then Q2W until disease progression or intolerable toxicity.[2]
†Based on DeLLphi-301 safety data of patients who received IMDELLTRA™ 10 mg (n=133) and those who received IMDELLTRA™ 100 mg (n=87).[2]

For severe or life-threatening CRS, recommend tocilizumab or equivalent therapy and admission in intensive care unit (ICU) for supportive therapy[1]

Please see the IMDELLTRA™ full Prescribing Information for guidelines on grading, dosage modifications, and management of CRS and neurologic toxicity, including ICANS.

Important Dosing Information:

- Administer IMDELLTRA™ according to the step-up dosing schedule to reduce the incidence and severity of CRS
- 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 ICANS
- Due to the risk of CRS and neurologic toxicity, including ICANS, patients 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 in an appropriate healthcare setting

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IQR, interquartile range; Q2W, every 2 weeks.

Please see additional Important Safety Information, including BOXED WARNINGS, on pages 14–15.

CRS dosage modifications and management

- Diagnose CRS based on clinical presentation (See page 2 under “Warnings”)[2]
- Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations below[1]
- Monitor patients who experience Grade 2 or higher CRS with continuous cardiac telemetry and pulse oximetry. Perform laboratory testing to monitor for DIC, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function.[2] Please see the full Prescribing Information for additional information

Dosage modifications and management strategies[2,‡]

Grade	Dosage Modifications	Management Strategies
Grade 1	Withhold IMDELLTRA™ until event resolves, then resume IMDELLTRA™ at the next scheduled dose	Administer symptomatic treatment (eg, acetaminophen) for fever
Grade 2	Withhold IMDELLTRA™ until event resolves, then resume IMDELLTRA™ at the next scheduled dose	• Recommend hospitalization for a minimum of 24 hours with cardiac telemetry and pulse oximetry • Administer symptomatic treatment (eg, acetaminophen) for fever • Administer supplemental oxygen and intravenous fluids (IVF) when indicated • Consider dexamethasone[§] (or equivalent) 8 mg IV • Consider tocilizumab (or equivalent) When resuming treatment at the next planned dose, monitor patients from the start of the IMDELLTRA™ infusion for 22 to 24 hours in an appropriate healthcare setting
Grade 3	• Withhold IMDELLTRA™ until event resolves, then resume IMDELLTRA™ at the next scheduled dose • For recurrent Grade 3 events, permanently discontinue IMDELLTRA™	In addition to Grade 2 treatment: • Recommend intensive monitoring (eg, ICU care) • Administer dexamethasone[§] (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) • Prior to the next dose, administer concomitant medications as recommended for Cycle 1 When resuming treatment at the next planned dose, monitor patients from the start of the IMDELLTRA™ infusion for 22 to 24 hours in an appropriate healthcare setting
Grade 4	Permanently discontinue IMDELLTRA™	• ICU care • Per Grade 3 treatment • Recommend tocilizumab (or equivalent)

‡CRS grading, dosage modifications, and management are based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).[2]
§Taper steroids per standard-of-care guidelines.[2]
DIC, disseminated intravascular coagulation; IV, intravenous.

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Understanding immune effector cell–associated neurotoxicity syndrome (ICANS)

ICANS is a disorder that may occur in the CNS following treatment with T-cell–engaging therapies due to the activation or engagement of endogenous or infused T cells and/or other immune effector cells.[3] IMDELLTRA™ can cause serious or life-threatening neurologic toxicity, including ICANS. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.[2]

- **ICANS grading is determined by the most severe events**[3]
- Clinical signs and symptoms of ICANS may include but are not limited to confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia[2]

Grading ICANS[2]

Grade*	Symptoms
Grade 1	• Immune Effector Cell–Associated Encephalopathy (ICE) score 7–9† with no depressed level of consciousness
Grade 2	• ICE score 3–6† and/or • Mild somnolence awaking to voice
Grade 3	• ICE score 0–2† 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
Grade 4	• ICE score 0† (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 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

ICE assessment tool[3]

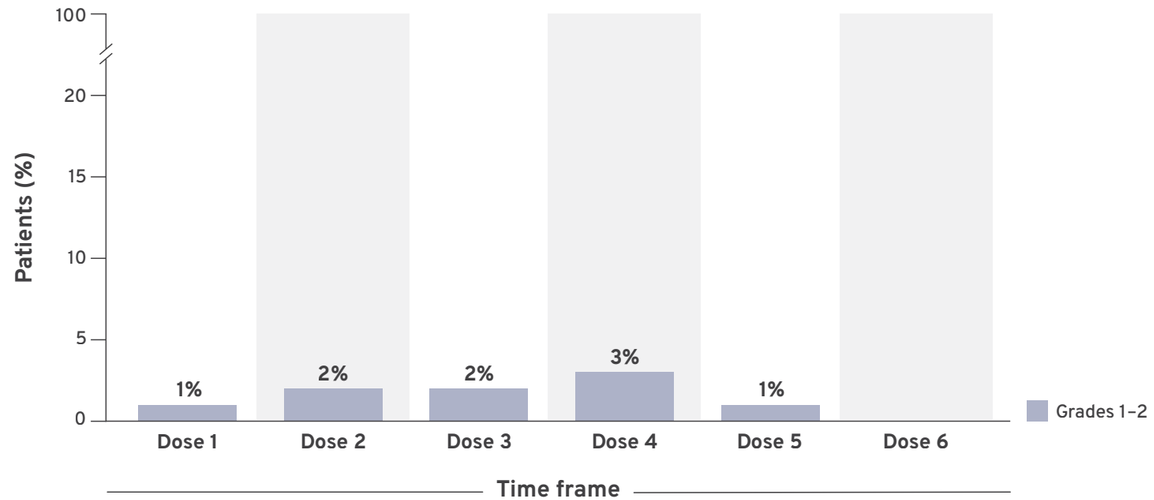
Assessment	Points
Orientation: Orientation to year, month, city, hospital	4
Naming: Ability to name 3 objects (eg, point to clock, pen, button)	3
Following commands: Ability to follow simple commands (eg, "show me 2 fingers" or "close your eyes and stick out your tongue")	1
Writing: Ability to write a standard sentence (eg, "our national bird is the bald eagle")	1
Attention: Ability to count backwards from 100 by 10	1

*Based on ASTCT Consensus Grading (2019).[2]
†If patient is arousable and able to perform ICE Assessment, assess: orientation (oriented to year, month, city, hospital = 4 points); naming (names 3 objects, eg, point to clock, pen, button = 3 points); following commands (eg, "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.[2]

ASTCT, American Society for Transplantation and Cellular Therapy; CNS, central nervous system; CRS, cytokine release syndrome; EEG, electroencephalogram.

Neurologic toxicity, including ICANS, occurred in 47% of patients with ES-SCLC treated with IMDELLTRA™[2,‡]

ICANS and associated neurologic events across treatment doses in the DeLLphi-301 study[4,§]



In the DeLLphi-300 and DeLLphi-301 pooled safety population:

- Neurologic toxicity, including ICANS, occurred in 47% of patients who received IMDELLTRA™, including 10% Grade 3[2,‡]
- ICANS occurred in 9% of IMDELLTRA™-treated patients[2,‡]
- Recurrent ICANS occurred in 1.6% of patients[2,‡]
- Most patients experienced ICANS following Cycle 2 Day 1 (24%). Following Day 1, Day 8, and Day 15 infusions, 0.5%, 0.5%, and 3.7% of patients experienced ≥ Grade 2 ICANS, respectively[2,‡]
- The most frequent neurologic toxicities were headache (14%), peripheral neuropathy (7%), dizziness (7%), insomnia (6%), muscular weakness (3.7%), delirium (2.1%), syncope (1.6%), and neurotoxicity (1.1%)[2,‡]

‡Based on the pooled safety population of 187 patients enrolled in DeLLphi-300 and DeLLphi-301 who received IMDELLTRA™ 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8, 15, and then Q2W until disease progression or intolerable toxicity.[2]
§Based on 133 patients who received IMDELLTRA™ 10 mg in the DeLLphi-301 study.[4]

ES-SCLC, extensive-stage small cell lung cancer; Q2W, every 2 weeks.

Please see additional Important Safety Information, including BOXED WARNINGS, on pages 14–15.

Onset and time to resolution of ICANS with IMDELLTRA™[2,*]

Median onset from the first dose of IMDELLTRA™

29.5 days

(1–154 days)

Median time to resolution

33 days

(1–93 days)

ICANS can occur several weeks following IMDELLTRA™ administration.[2]

*Based on the pooled safety population of 187 patients enrolled in DeLLphi-300 and DeLLphi-301 who received IMDELLTRA™ 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8, 15, and then Q2W until disease progression or intolerable toxicity.[2]

Provide supportive therapy, which may include intensive care, for severe or life-threatening neurologic toxicities, including ICANS[2]

Please see the IMDELLTRA™ full Prescribing Information for guidelines on grading, dosage modifications, and management of CRS and neurologic toxicity, including ICANS.

CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; Q2W, every 2 weeks.

Neurologic toxicity/ICANS dosage modifications and management

- At the first sign of neurologic toxicity, including ICANS, withhold IMDELLTRA™ and consider neurology evaluation[2]
- Closely monitor patients for signs and symptoms of neurologic toxicity and ICANS during IMDELLTRA™ treatment[2]
- Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care, for severe or life-threatening neurologic toxicities, including ICANS[2]
- Manage ICANS and neurologic toxicity according to the recommendations provided here.[1] Please see the full Prescribing Information for additional information.

Dosage modifications and management strategies[2,†]

Grade	Dosage Modifications	Management Strategies
ICANS Grade 1	Withhold IMDELLTRA™ until ICANS resolves, then resume IMDELLTRA™ at the next scheduled dose	Supportive care
ICANS Grade 2	Withhold IMDELLTRA™ until ICANS resolves, then resume IMDELLTRA™ at the next scheduled dose	• Supportive care • Dexamethasone[‡] (or equivalent) 10 mg IV. Can repeat every 6 hours or methylprednisolone 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 for 22 to 24 hours following the next dose of IMDELLTRA™
ICANS Grade 3	• Withhold IMDELLTRA™ until ICANS resolves, then resume IMDELLTRA™ at the next scheduled dose • If there is no improvement to Grade ≤ 1 within 7 days or Grade 3 toxicity reoccurs within 7 days of reinitiation, permanently discontinue IMDELLTRA™ • For recurrent Grade 3 events, permanently discontinue IMDELLTRA™	• Recommend intensive monitoring (eg, ICU care) • Consider mechanical ventilation for airway protection • Dexamethasone[‡] (or equivalent) 10 mg IV every 6 hours or methylprednisolone 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 for 22 to 24 hours following the next dose of IMDELLTRA™
ICANS Grade 4	Permanently discontinue IMDELLTRA™	• ICU care • Consider mechanical ventilation for airway protection • High-dose corticosteroids[‡] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent Grade ≥ 3 neurotoxicity • Treat convulsive status epilepticus per institutional guidelines

[†]ICANS grading, dosage modification, and management are based on ASTCT Consensus Grading (2019).[2]
[‡]Taper steroids per standard-of-care guidelines.[2]
ASTCT, American Society for Transplantation and Cellular Therapy; CT, computed tomography; ICU, intensive care unit; IV, intravenous; MRI, magnetic resonance imaging.

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Restarting IMDELLTRA™ after dosage delay

- If a dose of IMDELLTRA™ is delayed, restart therapy based on the recommendations here and resume the dosing schedule accordingly[2]
- Administer required concomitant medications as indicated.[2] (See pages 1 and 3 under Required Concomitant Medications for IMDELLTRA™ Administration for Cycle 1)

Dosage modifications[2]

Last Dose Administered	Time Since the Last Dose Administered	Action*
1 mg on Cycle 1 Day 1	2 weeks or less (≤ 14 days)	Administer IMDELLTRA™ 10 mg, then resume with the planned dosage 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 dosage schedule
10 mg on Cycle 1 Day 8	3 weeks or less (≤ 21 days)	Administer IMDELLTRA™ 10 mg, then resume with the planned dosage 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 dosage schedule
10 mg on Cycle 1 Day 15 and subsequent Cycles Q2W thereafter	4 weeks or less (≤ 28 days)	Administer IMDELLTRA™ 10 mg, then resume with the planned dosage 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 dosage schedule

*Administer recommended concomitant medications before and after Cycle 1 IMDELLTRA™ infusions and monitor patients accordingly.

Q2W, every 2 weeks.

Please see additional Important Safety Information, including BOXED WARNINGS, on pages 14–15.

AMGEN® Support+

CALL 866-264-2778
Monday to Friday, 9:00 AM to 8:00 PM ET,
or visit **AmgenSupportPlus.com.**

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- Verify patient's insurance plan coverage details

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- Provide payer-specific prior authorization forms

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Call Amgen SupportPlus at (866) 264-2778, Monday – Friday, 9:00 AM – 8:00 PM ET

The Amgen Patient Navigator is not part of a patient's treatment team and does not provide medical advice or case management services. The Amgen Patient Navigator does not administer Amgen medications. Patients should always consult their healthcare provider regarding medical decisions or treatment concerns.

AMGEN® Support+ | **Co-Pay Program**

Helping eligible patients save on out-of-pocket costs

The Amgen SupportPlus Co-Pay Program may help eligible patients with private or commercial insurance lower their out-of-pocket costs.
- Pay as little as **$0† out-of-pocket** for each dose
- Can be applied to deductible, co-insurance, and co-payment†
- No income eligibility requirement

Encourage your patients with private or commercial insurance to check eligibility and enroll at AmgenSupportPlus.com/copay

†Eligibility criteria and program maximums apply. See AmgenSupportPlus.com/copay for full Terms and Conditions.

What if my patient doesn't have private or commercial insurance?
Amgen SupportPlus can provide your patients with information about independent nonprofit foundations that may be able to help.‡

‡Eligibility for resources provided by independent nonprofit patient assistance programs is based on the nonprofit's criteria. Amgen has no control over these programs and provides information as a courtesy only.

HCP, healthcare professional.

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WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

- **Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving IMDELLTRA™. Initiate treatment with IMDELLTRA™ using the step-up dosing schedule to reduce the incidence and severity of CRS. Withhold IMDELLTRA™ until CRS resolves or permanently discontinue based on severity.**
- **Neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), including serious or life-threatening reactions, can occur in patients receiving IMDELLTRA™. Monitor patients for signs and symptoms of neurologic toxicity, including ICANS, during treatment and treat promptly. Withhold IMDELLTRA™ until ICANS resolves or permanently discontinue based on severity.**

WARNINGS AND PRECAUTIONS

- **Cytokine Release Syndrome (CRS):** IMDELLTRA™ can cause CRS including serious or life-threatening reactions. In the pooled safety population, CRS occurred in 55% of patients who received IMDELLTRA™, including 34% Grade 1, 19% Grade 2, 1.1% Grade 3 and 0.5% Grade 4. Recurrent CRS occurred in 24% of patients, including 18% Grade 1 and 6% Grade 2.

  Most events (43%) of CRS occurred after the first dose, with 29% of patients experiencing any grade CRS after the second dose and 9% of patients experiencing CRS following the third dose or later. Following the Day 1, Day 8, and Day 15 infusions, 16%, 4.3% and 2.1% of patients experienced ≥ Grade 2 CRS, respectively. The median time to onset of all grade CRS from most recent dose of IMDELLTRA™ was 13.5 hours (range: 1 to 268 hours). The median time to onset of ≥ Grade 2 CRS from most recent dose of IMDELLTRA™ was 14.6 hours (range: 2 to 566 hours).

  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 IMDELLTRA™ infusions as described in Table 3 of the Prescribing Information (PI) to reduce the risk of CRS. Administer IMDELLTRA™ in an appropriate health care 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. Counsel patients to seek medical attention should signs or symptoms of CRS occur.
- **Neurologic Toxicity, Including ICANS:** IMDELLTRA™ can cause serious or life-threatening neurologic toxicity, including ICANS. In the pooled safety population, neurologic toxicity, including ICANS, occurred in 47% of patients who received IMDELLTRA™, including 10% Grade 3. The most frequent neurologic toxicities were headache (14%), peripheral neuropathy (7%), dizziness (7%), insomnia (6%), muscular weakness (3.7%), delirium (2.1%), syncope (1.6%), and neurotoxicity (1.1%).

  ICANS occurred in 9% of IMDELLTRA™-treated patients. Recurrent ICANS occurred in 1.6% of patients. Most patients experienced ICANS following Cycle 2 Day 1 (24%). Following Day 1, Day 8, and Day 15 infusions, 0.5%, 0.5% and 3.7% of patients experienced ≥ Grade 2 ICANS, respectively. The median time to onset of ICANS from the first dose of IMDELLTRA™ was 29.5 days (range: 1 to 154 days). ICANS can occur several weeks following administration of IMDELLTRA™. The median time to resolution of ICANS was 33 days (range: 1 to 93 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, in the event of any neurologic symptoms until they resolve.

  Closely monitor patients for signs and symptoms of neurologic toxicity and ICANS during treatment. At the first sign of ICANS, immediately evaluate the patient and provide supportive therapy based on severity. Withhold IMDELLTRA™ or permanently discontinue based on severity.
- **Cytopenias:** IMDELLTRA™ can cause cytopenias including neutropenia, thrombocytopenia, and anemia. In the pooled safety population, decreased neutrophils occurred in 12% including 6% Grade 3 or 4 of IMDELLTRA™-treated patients. The median time to onset for Grade 3 or 4 neutropenia was 29.5 days (range: 2 to 213). Decreased platelets occurred in 33% including 3.2% Grade 3 or 4. The median time to onset for Grade 3 or 4 decreased platelets was 50 days (range: 3 to 420). Decreased hemoglobin occurred in 58% including 5% Grade 3 or 4. Febrile neutropenia occurred in 0.5% of patients treated with IMDELLTRA™.

  Monitor patients for signs and symptoms of cytopenias. Perform complete blood counts prior to treatment with IMDELLTRA™, before each dose, and as clinically indicated. Based on the severity of cytopenias, temporarily withhold, or permanently discontinue IMDELLTRA™.
- **Infections:** IMDELLTRA™ can cause serious infections, including life-threatening and fatal infections.

  In the pooled safety population, infections, including opportunistic infections, occurred in 41% of patients who received IMDELLTRA™. Grade 3 or 4 infections occurred in 13% of patients. The most frequent infections were COVID-19 (9%, majority during the COVID-19 pandemic), urinary tract infection (10%), pneumonia (9%), respiratory tract infection (3.2%), and candida infection (3.2%).

  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.
- **Hepatotoxicity:** IMDELLTRA™ can cause hepatotoxicity. In the pooled safety population, elevated ALT occurred in 42%, with Grade 3 or 4 ALT elevation occurring in 2.1%. Elevated AST occurred in 44% of patients, with Grade 3 or 4 AST elevation occurring in 3.2%. Elevated bilirubin occurred in 15% of patients; Grade 3 or 4 total bilirubin elevations occurred in 1.6% of patients. Liver enzyme elevation can occur with or without concurrent CRS. Monitor liver enzymes and bilirubin prior to treatment with IMDELLTRA™, before each dose, and as clinically indicated. Withhold IMDELLTRA™ or permanently discontinue based on severity.
- **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.
- **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.

ADVERSE REACTIONS

- The most common (> 20%) adverse reactions were CRS (55%), fatigue (51%), pyrexia (36%), dysgeusia (36%), decreased appetite (34%), musculoskeletal pain (30%), constipation (30%), anemia (27%), and nausea (22%). The most common (≥ 2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes (57%), decreased sodium (16%), increased uric acid (10%), decreased total neutrophils (6%), decreased hemoglobin (5%), increased activated partial thromboplastin time (5%), decreased potassium (5%), increased aspartate aminotransferase (3.2%), decreased white blood cells (3.8%), decreased platelets (3.2%), and increased alanine aminotransferase (2.1%).
- Serious adverse reactions occurred in 58% of patients. Serious adverse reactions in > 3% of patients included CRS (24%), pneumonia (6%), pyrexia (3.7%), and hyponatremia (3.6%). Fatal adverse reactions occurred in 2.7% of patients including pneumonia (0.5%), aspiration (0.5%), pulmonary embolism (0.5%), respiratory acidosis (0.5%), and respiratory failure (0.5%).

DOSAGE AND ADMINISTRATION: Important Dosing Information

- Administer IMDELLTRA™ as an intravenous infusion over one hour.
- Administer IMDELLTRA™ according to the step-up dosing schedule in the IMDELLTRA™ PI (Table 1) to reduce the incidence and severity of CRS.
- For Cycle 1, administer recommended concomitant medications before and after Cycle 1 IMDELLTRA™ infusions to reduce the risk of CRS reactions as described in the PI (Table 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 ICANS.
- 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.
- Recommend that patients remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA™ following Cycle 1 Day 1 and Cycle 1 Day 8 doses, accompanied by a caregiver.
- Prior to administration of IMDELLTRA™, evaluate complete blood count, liver enzymes, and bilirubin before each dose, and as clinically indicated.
- Ensure patients are well hydrated prior to administration of IMDELLTRA™.

Please see IMDELLTRA™ full Prescribing Information, including BOXED WARNINGS.

CRS and ICANS

- **CRS** is an acute systemic inflammatory response to immunotherapy characterized by fever and multiple organ dysfunction.[1] IMDELLTRA™ can cause CRS, including serious or life-threatening reactions[2]
  - Closely monitor patients for signs and symptoms of CRS. If CRS is suspected, manage according to the recommendations in the full Prescribing Information; withhold or permanently discontinue based on severity[2]
- **ICANS** is a disorder that may occur in the CNS following treatment with T-cell–engaging therapies due to the activation or engagement of endogenous or infused T cells and/or other immune effector cells.[3] IMDELLTRA™ can cause serious or life-threatening neurologic toxicity, including ICANS. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS[2]
  - Closely monitor patients for signs and symptoms of neurologic toxicity and ICANS during treatment. At the first sign of neurologic toxicity, including ICANS, withhold IMDELLTRA™ and consider neurology evaluation[2]

In the DeLLphi-300 and DeLLphi-301 pooled safety population:

- 55% (n=103/187) of patients who received IMDELLTRA™ experienced any Grade CRS[2,*]
- 34% (n=64/187), 19% (n=36/187), 1.1% (n=2/187), and 0.5% (n=1/187) of patients experienced Grade 1, 2, 3, and 4 CRS, respectively[2,*]
- Recurrent CRS occurred in 24% of patients treated with IMDELLTRA™, including 18% Grade 1 and 6% Grade 2[2,*]
- ICANS occurred in 9% of patients treated with IMDELLTRA™. Recurrent ICANS occurred in 1.6% of patients[2,*]
- Following Day 1, Day 8, and Day 15 infusions, 0.5%, 0.5%, and 3.7% of patients experienced ≥ Grade 2 ICANS, respectively[2,*]

*Based on the pooled safety population of 187 patients enrolled in DeLLphi-300 and DeLLphi-301 who received IMDELLTRA™ 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8, 15, and then Q2W until disease progression or intolerable toxicity.[2]

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

- **Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving IMDELLTRA™. Initiate treatment with IMDELLTRA™ using the step-up dosing schedule to reduce the incidence and severity of CRS. Withhold IMDELLTRA™ until CRS resolves or permanently discontinue based on severity.**
- **Neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), including serious or life-threatening reactions, can occur in patients receiving IMDELLTRA™. Monitor patients for signs and symptoms of neurologic toxicity, including ICANS, during treatment and treat promptly. Withhold IMDELLTRA™ until ICANS resolves or permanently discontinue based on severity.**

Please see additional Important Safety Information on pages 14–15.

Visit IMDELLTRAhcp.com for more information

CNS, central nervous system; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; Q2W, every 2 weeks.

References: 1. Shimabukuro-Vornhagen A, et al. *J Immunother Cancer.* 2018;6:56. **2.** IMDELLTRA™ (tarlatamab-dlle) prescribing information, Amgen. **3.** Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625-638. **4.** Ahn M-J, et al. *N Engl J Med.* 2023;389(22):2063-2075. **5.** Ahn M-J, et al. *N Engl J Med.* 2023;389(suppl):2063-2075.

AMGEN

IMDELLTRA™ (tarlatamab-dlle) for injection 1 mg & 10 mg single-use vials