

REVIEW ARTICLE

Practical management of adverse events in patients receiving tarlatamab, a delta-like ligand 3-targeted bispecific T-cell engager immunotherapy, for previously treated small cell lung cancer

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Abstract

Tarlatamab is a bispecific T-cell engager immunotherapy targeting delta-like ligand 3 (DLL3) and the cluster of differentiation 3 (CD3) molecule. In the phase 2 DeLLphi-301 trial of tarlatamab for patients with previously treated small cell lung cancer, tarlatamab 10 mg every 2 weeks achieved durable responses and encouraging survival outcomes. Analyses of updated safety data from the DeLLphi-301 trial demonstrated that the most common treatment-emergent adverse events were cytokine release syndrome (53%), pyrexia (38%), decreased appetite (36%), dysgeusia (32%), and anemia (30%). Cytokine release syndrome was mostly grade 1 or 2 in severity, occurred primarily after the first or second tarlatamab dose, and was managed with supportive care, which included the administration of antipyretics (e.g., acetaminophen), intravenous hydration, and/or glucocorticoids. Other treatment-emergent adverse effects of interest included neutropenia (16%) and immune effector cell-associated neurotoxicity syndrome and associated neurologic events (10%). Given that tarlatamab is the first T-cell engager approved for the treatment of small cell lung cancer, raising awareness with regard to the monitoring and management of tarlatamab-associated adverse events is essential. Here, the authors describe the timing, occurrence, and duration of these adverse events and review the management and risk-mitigation strategies used by clinical investigators during the DeLLphi-301 trial.

KEYWORDS

adverse event management, DeLLphi-301, safety profile, tarlatamab

INTRODUCTION

Tarlatamab is a bispecific T-cell engager (BiTE) immunotherapy that binds both delta-like ligand 3 (DLL3) on cancer cells and the cluster of differentiation 3 (CD3) molecule on T cells. Tarlatamab causes T-cell activation, release of inflammatory cytokines, and lysis of DLL3-expressing cells.¹ Tarlatamab received accelerated approval from the US Food and Drug Administration in May 2024 for the treatment of patients with extensive-stage small cell lung cancer (ES-SCLC) who had disease progression on or after platinum-based chemotherapy based on the durable responses and manageable safety profile observed in the DeLLphi-301 phase 2 trial.^{2,3} Here, we provide an overview of the safety profile of tarlatamab 10 mg with updated data from the DeLLphi-301 trial (data cutoff, October 2, 2023). Details on the timing, occurrence, and duration of adverse events (AEs) are reported. We also provide clinical insights and strategies for AE management to optimize the long-term patient treatment experience.

OVERVIEW OF THE SAFETY PROFILE OF TARLATAMAB IN THE DeLLphi-301 TRIAL

In the phase 2 DeLLphi-301 trial in patients with previously treated SCLC, 133 patients received at least one dose of tarlatamab 10 mg. The most common treatment-emergent AEs (TEAEs; incidence, $\geq 20\%$ of patients) were cytokine release syndrome (CRS; 53%), pyrexia

(38%), decreased appetite (36%), dysgeusia (32%), anemia (30%), constipation (29%), asthenia (25%), and fatigue (24%; see Table S1). Other TEAEs of interest were neutropenia (16%) and immune effector cell-associated neurotoxicity syndrome (ICANS; 10%). The most common grade ≥ 3 TEAEs were lymphopenia (13.5%), anemia (8%), hyponatremia (6%), and neutropenia (6%; see Table S2). The time to onset of key AEs from the first tarlatamab dose is illustrated in Figure 1. CRS, fatigue, and ICANS were observed early, whereas the onset of neutropenia was relatively delayed (Figure 1). Treatment-related AEs led to dose interruption in 15% of patients and discontinuation in 3% of patients.

Cytokine release syndrome

Given the mechanism of action of BiTE immunotherapies, the safety profile of tarlatamab includes CRS.^{4,5} CRS is a systemic inflammatory response caused by the activation of T cells and the subsequent release of inflammatory cytokines, such as interferon gamma.⁴ CRS diagnosis has often been considered a diagnosis of exclusion. Fever is considered the defining symptom of CRS, which can evolve to present with hypoxia, hypotension, tachypnea, headache, tachycardia, and rash (see Table S3).⁶ CRS can progress to include potentially life-threatening complications and end organ damage. This presents a diagnostic challenge because the differential diagnosis of fever is broad and can be caused by other conditions, particularly in patients with cancer,

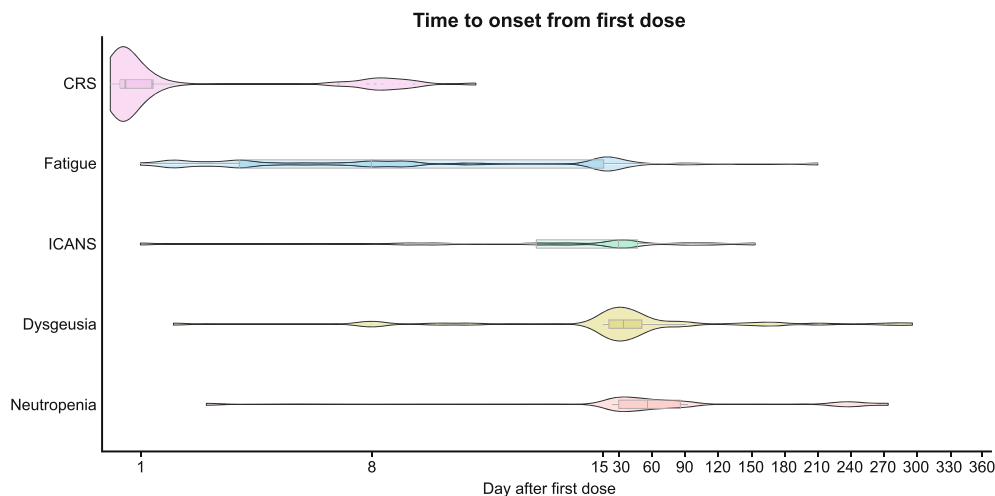


FIGURE 1 Time of adverse event onset from the first tarlatamab dose. Violin box plot showing the time to onset of some of the most common treatment-emergent adverse events from the first dose of tarlatamab in the DeLLphi-301 trial. The median time to onset and the interquartile range are indicated within each plot, with the breadth of the violin box plot indicating the patient distribution at any particular time point and the height proportional to the incidence rate of each event. The x-axis has a variable scale. CRS indicates cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome and associated neurologic events.

including, but not limited to, infection, hypersensitivity, hemophagocytic lymphohistiocytosis, and tumor lysis syndrome.^{7–10} CRS is graded using the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria based on the presentation of fever and the severity of hypoxia and hypotension.⁶ It should be noted, however, that the incidence and severity of CRS are lower with BiTE therapies relative to chimeric antigen receptor T-cell therapies.^{11–15}

CRS in the DeLLphi-301 trial

In the DeLLphi-301 trial, CRS occurred in 70 of 133 patients (53%) who received tarlatamab 10 mg (Table 1). CRS predominantly occurred after the first or second tarlatamab dose. CRS was reported in 54 of 133 patients (41%) after the first dose and in 39 of 133 patients (29%) after the second dose (Figure 2). Three of 133 patients (2%) experienced CRS at cycle 2 or later; each of these three patients had missed one or more doses during cycle 1 and had resumed treatment in cycle 2. The most common CRS symptom, other than fever, was hypotension (14 of 70 patients; 20%; Table 1). CRS was predominantly grade 1 (42 of 70 patients; 60%) or grade 2 (fever with hypoxia and/or hypotension not requiring vasopressors; 27 of 70 patients; 39%), and one patient (1.4%) experienced grade 3 CRS (Table 2). There were no grade 4 or 5 CRS events. The median time to CRS onset from the first tarlatamab dose was 13.7 hours (interquartile range [IQR], 9.3–33.2; Figure 1). The median time to resolution (Kaplan–Meier estimate) was 3 days (IQR, 2–5 days). The median time to onset of grade ≥ 2 CRS from the last prior tarlatamab dose was 15.4 hours (IQR, 9.6–27.9 hours). Patients whose fever persisted for several hours, regardless of whether it subsided on antipyretic therapy, were more likely to experience a grade 2 or higher CRS event.

Recurrent CRS occurred in 33 of 133 patients (25%). All patients with recurrent CRS had experienced their first CRS event during cycle 1. Recurrent CRS primarily occurred in cycle 1 and was grade 1 (88%) or grade 2 (12%; Table 3).

CRS led to dose interruption in four of 70 patients (6%). No patient discontinued tarlatamab because of CRS. One patient with concurrent grade 3 CRS died from respiratory failure. The respiratory failure was assessed by the investigator to be treatment-related, although this categorization was confounded by the presence of other contributing factors, including baseline chronic obstructive pulmonary disease requiring supplemental oxygen, baseline compromised pulmonary functional reserve, concurrent grade 3 CRS and pneumonitis after cycle 1 day 1 (C1D1) treatment, and a decision against escalation to an intensive care unit level of care.

CRS management in the DeLLphi-301 trial

When a patient presented with fever ($\geq 38^{\circ}\text{C}$), a thorough work-up to rule out other causes (infection or sepsis) was performed. If CRS was suspected, the CRS event was graded according to the ASTCT consensus grading and was treated based on the grade (Table 4).^{2,6} The management of CRS in the DeLLphi-301 trial protocol is described in detail in Table 4. Of note, clinical trial sites were required to have medications for treating CRS available on site, including glucocorticoids and tocilizumab or siltuximab, if tocilizumab was not available.

Because CRS in the DeLLphi-301 trial was predominantly grade 1 or grade 2 in severity, it was generally managed with supportive care that included antipyretics (e.g., acetaminophen), intravenous hydration, and/or glucocorticoid use. Additional interventions, such as tocilizumab (used in eight of 70 patients), supplemental high-flow

TABLE 1 Incidence of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome symptoms in the DeLLphi-301 trial, N = 133.

CRS/ICANS symptoms	Tarlatamab 10 mg: No. (%) ^a
No. of patients reporting CRS	70 (52.6)
Any CRS symptom	70 (100.0)
Fever, temperature $\geq 38^{\circ}\text{C}$	68 (97.1)
Hypotension	14 (20.0)
Hypoxia	11 (15.7)
Headache	9 (12.9)
Nausea	7 (10.0)
Fatigue	7 (10.0)
Tachycardia	6 (8.6)
Rigors	6 (8.6)
Myalgia	5 (7.1)
Vomiting	4 (5.7)
Malaise	3 (4.3)
Arthralgia	3 (4.3)
Anorexia	2 (2.9)
Tremor	2 (2.9)
No. of patients reporting ICANS ^b	7 (5.3)
Any ICANS symptom	6 (85.7)
Confusion	4 (57.1)
Impaired attention	3 (42.9)
Motor weakness/findings	1 (14.3)
Dysgraphia	1 (14.3)
Increased tone	1 (14.3)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome and associated neurologic events.

^aPercentages for patients reporting CRS/ICANS events are based on the number of patients in the safety analysis set. Percentages for patients reporting symptoms were calculated by using the number of patients reporting CRS or ICANS events as the denominator. The safety analysis set includes all patients who received at least one dose of tarlatamab.

^bPatients with ICANS-only symptoms; patients with associated neurologic events were not included here.

oxygen (>6 liters per minute; one of 70 patients), and/or vasopressor support (one of 70 patients), were infrequently required (see Table S4); siltuximab was not used. The incidence and duration of hospitalization for serious CRS are detailed in Table 5.

Immune effector cell-associated neurotoxicity syndrome

The pathophysiology of ICANS remains poorly understood. Increased production of proinflammatory cytokines may lead to the activation

of endothelial cells, increased permeability of the blood–brain barrier, and elevated levels of cytokines in the cerebrospinal fluid.¹⁶ Signs and symptoms vary and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.⁶ According to the ASTCT grading system, ICANS is graded using a combination of the immune effector cell-associated encephalopathy (ICE) score, level of consciousness, motor findings, seizure assessment, and intracranial pressure level or extent of cerebral edema (see Tables S5 and S6).⁶ ICANS is also a diagnosis of exclusion. Symptoms of ICANS can appear similar to symptoms observed with infection/sepsis, stroke, paraneoplastic syndromes, the use of pain medications, and new or progressive disease in the central nervous system.⁷

ICANS in the DeLLphi-301 trial

Because ICANS can have a wide range of manifestations with nonspecific symptoms, associated neurologic events were included in the reporting of ICANS¹⁷ (for the list of associated neurologic events, see Table S7). In the DeLLphi-301 trial, ICANS and associated neurologic events (henceforth referred to as ICANS) occurred in 13 of 133 patients (10%) who were treated with tarlatamab 10 mg (Table 2). Patients with ICANS reported symptoms that included confusion, impaired attention, motor weakness/findings, dysgraphia, and increased tone (Table 1). All ICANS events were grade 1 (seven of 13 patients; 54%) or grade 2 (six of 13 patients; 46%) in severity (Table 2) and mostly occurred during cycle 1 or 2. (Figure 2). Of the 13 patients with ICANS, the median time to onset from the first tarlatamab dose was 30 days (IQR, 13–47 days), and the median time to resolution was 33 days (IQR, 4–93 days; Kaplan–Meier estimate; Figure 1). ICANS events that included confusion or impaired attention symptoms (11 of 16 events) were shorter in duration (median time to resolution, 8 days; IQR, 3–33 days), whereas ICANS events characterized by low-grade muscular weakness symptoms (five of 16 events) generally took longer to resolve (median time to resolution, 69 days; IQR, 42 days to not estimable).

ICANS led to dose interruption in one patient and discontinuation in one patient. No deaths from ICANS were reported. Two patients were hospitalized for serious ICANS after the first or second dose of tarlatamab, and two patients were hospitalized for serious ICANS after a third or later dose of tarlatamab. The frequency and duration of hospitalization for serious ICANS are detailed in Table 5. In a subgroup analysis, ICANS occurred in three of 22 patients (14%) with brain metastases and in five of 77 patients (6%) without brain metastases.¹⁸ All events were grade 1 or 2 in severity.

ICANS management in the DeLLphi-301 trial

Patients in the DeLLphi-301 trial were monitored for clinical signs or symptoms that could be suggestive of ICANS, including confusion, impaired attention, aphasia, tremor, and muscle weakness. It was

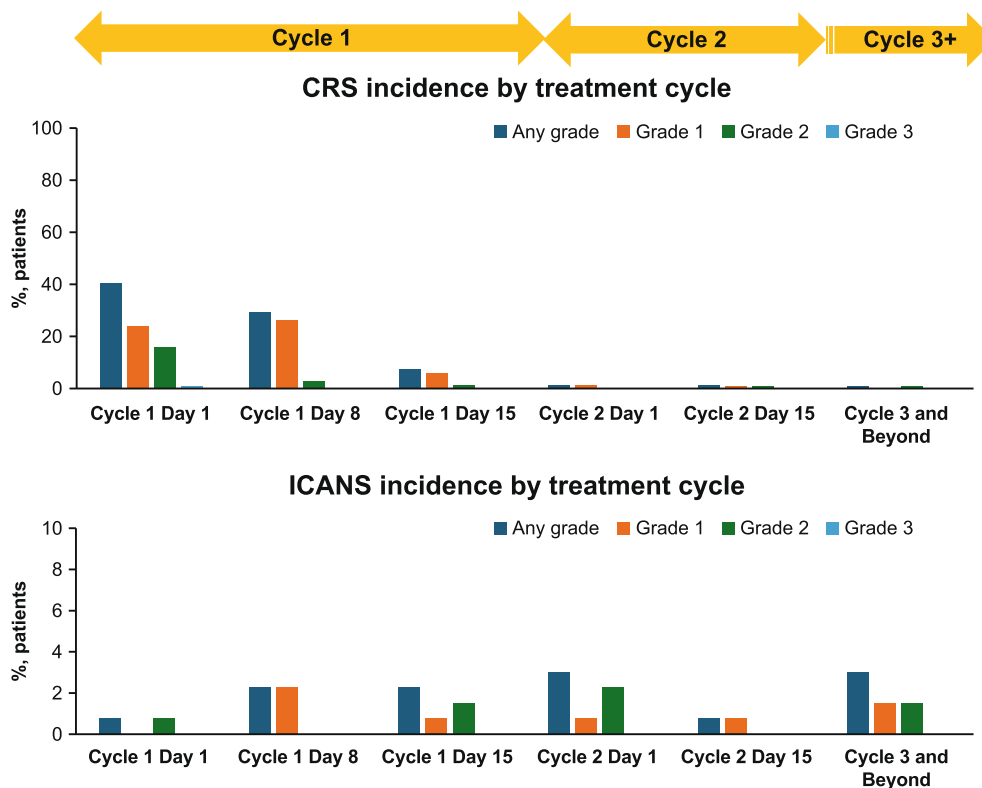


FIGURE 2 The incidence of CRS and ICANS by cycle and grade. The incidence of CRS and ICANS according to severity and treatment cycle are shown for patients in the 10-mg tarlatamab dose cohort. During the first cycle, CRS was reported by 54 of 133 patients (41%) after the first tarlatamab dose (days 1–7), by 39 of 133 patients (29%) after the day-8 dose (days 8–14), and by 10 of 133 patients (8%) after the day-15 dose (days 15–28). CRS events were identified on the basis of a narrow search for preferred terms in MedDRA version 26.1 and were graded according to the American Society for Transplantation and Cellular Therapy 2019 consensus criteria. During the first cycle, ICANS was reported in one of 133 patients (<1%) after the first tarlatamab dose (days 1–7), in three of 133 patients (2%) after the day-8 dose (days 8–14), and in three of 133 patients (2%) after the day-15 dose (days 15–28). ICANS data include associated neurologic events identified on the basis of a broad search for 61 preferred terms in MedDRA. CRS indicates cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome and associated neurologic events; MedDRA, Medical Dictionary for Regulatory Activities.

important to rule out other neurologic etiologies, such as epilepsy, infectious disease, progression of central nervous system metastasis, side effects of other concomitant medications, or electrolyte disturbances within or outside the context of paraneoplastic syndromes. In the DeLLphi-301 trial, neurologic examinations were performed as clinically indicated on or after dose administration. Although there were no grade 3 ICANS events in this trial, the protocol recommended a neurology consultation at the first sign of neurotoxicity and brain imaging for patients with persistent grade ≥ 3 neurotoxicity, with consideration for repeat neuroimaging (computed tomography or magnetic resonance imaging) every 2–3 days. Electroencephalograms were required for the assessment of any seizure activity that was grade ≥ 2 . If ICANS was suspected, the next step involved using the ICE assessment tool (see Table S6) and the ASTCT ICANS consensus grading criteria (see Table S5). Management strategies for ICANS used in the DeLLphi-301 trial are listed in Table 6. Briefly, grade 1 and 2 ICANS were to be managed by supportive care (grade 1) or steroids (grade 2). Steroids that were used included dexamethasone (10 mg intravenously), repeated every 6 hours if symptoms worsened, or methylprednisolone (1 mg/kg

intravenously every 12 hours if symptoms worsened). For more severe events (grade ≥ 3) respiratory assistance with mechanical ventilation for airway protection (for grade 3 events) and treatment of status epilepticus according to institutional guidelines (for grade 4 events) were recommended, although this was never required in the DeLLphi-301 trial (for details, see Table 6). If grade ≥ 3 CRS with hypotension was also present, intravenous tocilizumab 8 mg/kg over 1 hour (not exceeding 800 mg per dose) was considered.

STRATEGIES TO MITIGATE THE RISK OF DEVELOPING CRS AND ICANS USED IN THE DeLLphi-301 TRIAL

Pretreatment evaluation

Before treatment in the DeLLphi-301 trial, patients received physical and neurologic examinations and laboratory testing that included a complete blood count, blood chemistry panel testing, and quantitation of C-reactive protein levels. Baseline hematologic, renal, hepatic,

TABLE 2 Summary of tarlatamab administration, cytokine release syndrome mitigation strategies, timing, and incidence of cytokine release syndrome and immune effector cell-associated neurotoxicity in the DeLLphi-301 trial.

Summary	Tarlatamab 10 mg
Route of administration	Intravenous administration over 60 minutes (250 mL/hour)
Pump	Infusion pump using constant flow rate. The pump should be programmable, lockable, and nonelastomeric with an alarm
Dosing schedule	Cycle 1, days 1, 8, and 15 Cycle 2 onward (once every 2 weeks until disease progression)
CRS mitigation strategies	
Step up dosing	Cycle 1 day 1: 1 mg Cycle 1 days 8 and 15: 10 mg Cycle 2 onward: 10 mg once every 2 weeks
Prophylactic medications	- Dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) administered within 1 hour before tarlatamab infusion on days 1 and 8 of cycle 1 only - IV hydration (1 liter of normal saline over 4–5 hours) administered immediately after all tarlatamab doses in cycle 1 (days 1, 8, and 15)
Hospitalization	- Hospitalization required after tarlatamab infusion on cycle 1 days 1 and 8^a - Cycle 1 day 15 and cycle 2: Hospitalization not required^b; monitoring for 6–8 hours after infusion - Cycles 3 and 4: Hospitalization not required; monitoring for 4 hours after infusion - Cycles ≥5: Hospitalization not required; monitoring for at least 2 hours after infusion
CRS severity: No. of patients/total no. of patients experiencing CRS (%)	Grade 1, 42/70 (60.0) Grade 2, 27/70 (39.0) Grade 3, 1/70 (1.0) Grade 4, 0 (0.0) Grade 5, 0 (0.0)
Timing of CRS events	
Time to onset of first CRS event from first tarlatamab dose: Median [IQR], hours	13.7 [9.3–33.2]
Time to onset of first CRS event from last prior tarlatamab dose: Median [IQR], hours	15.4 [9.5–28.1]
Time to onset of grade ≥2 CRS from last prior tarlatamab dose: Median [IQR], hours	15.4 [9.6–27.9]
Time to resolution of CRS, Kaplan-Meier estimate: Median [IQR], days	3 [2–5]
Severity of ICANS: No. of patients/total no. of patients experiencing ICANS (%)	Grade 1, 7/13 (54.0) Grade 2, 6/13 (46.0) Grade 3, 0 (0.0) Grade 4, 0 (0.0) Grade 5, 0 (0.0)
Time to onset of first ICANS event from first tarlatamab dose: Median [IQR], days	30 [13–47]
Time to onset of first ICANS event from last prior tarlatamab administration after each dose: Median [IQR], days	3 [1–7]
Time to resolution of ICANS presenting as muscular weakness: Median [IQR], days	69 [42 to not estimable]

TABLE 2 (Continued)

Summary	Tarlatamab 10 mg
Time to resolution of ICANS events, excluding muscular weakness: Median [IQR], days	8 [3–33]
Time to resolution of ICANS, Kaplan–Meier estimate: Median [IQR], days	33 [4–93]

Abbreviations: CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome and associated neurologic events; IQR, interquartile range.

^aPatients in parts 1 and 2 of the trial (n = 99) were monitored for 48 hours after tarlatamab infusion in cycle 1. Patients in part 3 (n = 34) were monitored for 24 hours during cycle 1 after tarlatamab infusion.

^bHospitalization was not required for cycle 1 day 15 doses unless the patient experienced any grade CRS or neurological events after cycle 1 day 1 or cycle 1 day 8 doses, in which case a 48-hour hospitalization was required after the cycle 1 day 15 dose.

TABLE 3 Frequency of patients experiencing one or more cytokine release syndrome event in the DeLLphi-301 trial.

CRS incidence	Tarlatamab 10 mg, N = 133						
Initial CRS event ^a	Grade 1	Grade 2		Grade 3		Total	
Patients, no. (%)	42 (60.0)	27 (39.0)		1 (1.0)		70 (53.0)	
Second CRS event with subsequent dose in cycle 1	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2	Total
Patients, no. (%)	20 (15.0)	3 (2.3)	9 (6.8)	1 (0.8)	0 (0.0)	0 (0.0)	33 (25.0)

Abbreviation: CRS, cytokine release syndrome.

^aGrade shown for the initial CRS event is the worst grade after the dose at which the first CRS event occurred.

pulmonary, and cardiac functions were also assessed before the first dose of tarlatamab.

Step-up dosing

Step-up dosing involves starting with a lower dose and escalating to the target dose to gradually prime the immune system and reduce the risk and/or severity of CRS.¹⁹ In the DeLLphi-301 trial, tarlatamab was administered as a step-up dose of 1 mg on C1D1, followed by 10 mg tarlatamab on C1D8 and C1D15. Thereafter, patients received 10 mg tarlatamab every 2 weeks until they developed disease progression or unacceptable toxicity. If tarlatamab administration was delayed, the protocol defined restart guidelines for neurologic events, CRS, tumor lysis syndrome, nonfebrile neutropenia, pituitary gland dysfunction, and hepatotoxicity. For all other treatment interruptions and delays, the protocol outlined restart guidelines, as described in Table S8.

Concomitant medications

Prophylactic administration of corticosteroids has been shown to lower the incidence and severity of CRS and ICANS.^{12,20,21} In addition, intravenous hydration may prevent an escalation in the severity of CRS by offsetting the effects of any potential hypotension.²² In the DeLLphi-301 trial, patients received intravenous dexamethasone 8 mg (or equivalent) within 1 hour before tarlatamab infusion on C1D1 and C1D8. Patients also received intravenous hydration (1 liter normal saline over 4–5 hours) immediately after all tarlatamab doses in cycle 1.

Postinfusion monitoring

For the dose-evaluation (part 1) and dose-expansion (part 2) parts of the DeLLphi-301 trial,² all patients received their C1D1 and C1D8 doses in the hospital and remained hospitalized for 48 hours for observation and AE monitoring. Hospitalization was not required on C1D15 unless the patient had experienced any grade CRS or neurologic events after the C1D1 or C1D8 doses; otherwise, the patient was observed for 8 hours after infusion (Table 2). The frequency at which vital signs were assessed during hospitalization is detailed in Table S9. Hospitalization requirements from treatment cycle 2 and later are detailed in Table 2.

In part 3—the reduced hospitalization substudy—patients were monitored for 24 hours (at either an inpatient unit or an outpatient infusion center) after the first two doses of tarlatamab (on C1D1 and C1D8). Vital signs were assessed as indicated in Table S9. Patients who experienced grade ≥2 CRS or grade ≥1 ICANS after the C1D1 and C1D8 infusions had increased additional hospitalization requirements. Patients were observed for 6–8 hours if they were not hospitalized. CRS was graded and treated as described previously and as indicated in Table 4. The safety profile in patients who were monitored for 24 hours postinfusion during cycle 1 was generally similar to that in patients who were monitored for 48 hours postinfusion.²

Posthospitalization requirements for the reduced hospitalization substudy

Discharged patients were asked to stay within 1 hour of travel from the site for 48 hours and within 1 hour of a hospital for 72 hours after the C1D1 and C1D8 doses. A home companion was required for

TABLE 4 Management approach for cytokine release syndrome as used in the DeLLphi-301 trial protocol.

CRS grade ^a	Defining symptoms	Management ^a	Dose modification
Grade 1	Symptoms require symptomatic treatment only Fever $\geq 38^{\circ}\text{C}$, without hypotension or hypoxia	Symptomatic treatment (e.g., paracetamol/acetaminophen) for fever	No treatment interruption needed
Grade 2	Symptoms require and respond to moderate intervention - Fever $\geq 38^{\circ}\text{C}$, - Hypotension not requiring vasopressors, and/or - Hypoxia requiring low-flow nasal cannula or blow-by	- Manage as for grade 1 - Supplemental oxygen when oxygen saturation $< 90\%$ on room air - IV fluids when SBP < 85 mmHg and/or persistent tachycardia (heart rate > 120 bpm) or symptomatic (e.g., dizziness/light-headedness) - Consider a single dose of dexamethasone 8 mg IV (or equivalent) - Consider tocilizumab^b (or equivalent)	Interrupt tarlatamab until event improves to CRS grade ≤ 1, then restart tarlatamab at the same dose level; discontinue if there is no improvement to CRS grade ≤ 1 within 7 days
Grade 3	Severe symptoms defined as temperature $\geq 38^{\circ}\text{C}$ with: - Hemodynamic instability requiring a vasopressor (with or without vasopressin) or - Worsening hypoxia or respiratory distress requiring high-flow nasal cannula (> 6 liters/minute oxygen) or face mask	- Manage as for grade 2 - Supplemental oxygen - Vasopressor with or without vasopressin - IV dexamethasone (or equivalent), and/or - Tocilizumab^b (siltuximab [11 mg/kg] administered over 1 hour as an intravenous infusion, may be used if tocilizumab is not available)	- Interrupt tarlatamab for at least 3 days until the event improves to CRS grade ≤ 1 - If there is no improvement to grade ≤ 1 within 7 days or if grade 3 toxicity re-occurs within 7 days of re-initiation, permanently discontinue tarlatamab
Grade 4	Life-threatening symptoms defined as temperature $\geq 38^{\circ}\text{C}$ with: - Hemodynamic instability requiring multiple vasopressors (excluding vasopressin) - Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)	- Manage as for grade 3 - Supplemental oxygen (positive pressure) - Multiple vasopressors - IV dexamethasone (or equivalent) - Tocilizumab^b (siltuximab [11 mg/kg] administered over 1 hour as an intravenous infusion, may be used if tocilizumab is not available)	Permanently discontinue tarlatamab

Abbreviations: BiPAP, bilevel positive airway pressure; bpm, beats per minute; CPAP, continuous positive airway pressure; CRS, cytokine response syndrome; IV, intravenous; SBP, systolic blood pressure.

^aBased on the American Society for Transplantation and Cellular Therapy consensus grading (2019).⁶

^bIn the DeLLphi-301 trial, the recommended tocilizumab dose was 8 mg/kg IV over 1 hour (not exceeding 800 mg/dose). Tocilizumab was repeated every 8 hours as needed if a patient was not responsive to IV fluids or to increasing supplemental oxygen and was limited to a maximum of three doses in a 24-hour period with a maximum total of four doses.

72 hours after the C1D1 and C1D8 infusions. These considerations allowed for close monitoring, early detection of CRS, and prompt management if needed.

Dysgeusia

The neuroendocrine transcription factor *ASCL1* drives the late-stage differentiation of certain types of taste bud cells.²³ Because *ASCL1* also regulates *DLL3* expression,²⁴ it can be speculated that these taste bud cells express *DLL3*. Tarlatamab may lead to T-cell-mediated destruction of these *DLL3*-expressing taste bud cells, causing dysgeusia.

In the DeLLphi-301 trial, dysgeusia was reported in 42 of 133 patients (32%), with a median time to onset of 34 days (IQR, 21–51 days; Figure 1).^{23,24} Within the study protocol, no recommendations were provided for the management of dysgeusia. Some DeLLphi-301 investigators used previously published strategies for managing dysgeusia.²⁵ These strategies include nutritional counseling from a registered dietitian and maintenance of good oral dental hygiene (thorough brushing of teeth at least twice a day). Other published strategies include maintenance of adequate hydration by drinking a minimum of 1.5–2 liters of energy-free beverages, such as water or unsweetened tea, per day; periodic chewing of cardamom; and inhaling the smell of cloves and lemon at least twice a day for about 15 seconds.²⁵

TABLE 5 Hospitalization details for patients experiencing serious cytokine response syndrome and immune effector cell-associated neurotoxicity syndrome and associated neurologic events in the DeLLphi-301 trial.

	Tarlatamab 10 mg	
	Parts 1 and 2, N = 99	Part 3, N = 34
Protocol-mandated hospitalization duration for first two doses of tarlatamab	48 hours	24 hours
Hospitalization after the first or second dose of tarlatamab: Cycle 1 day 1 to cycle 1 day 14		
Reported at least one serious CRS event, no. (%) ^a	22 (22.2)	5 (14.7)
Median duration of hospitalization, days	4.0	2.5
Reported at least one serious ICANS, no. (%) ^{b,c}	0 (0.0)	2 (5.9)
Median duration of hospitalization, days	NA	7.0
Hospitalization after the third or later dose of tarlatamab: Cycle 1 day 15 and beyond		
Reported at least one serious CRS event with hospitalization, no. (%)	6 (6.1)	0 (0.0)
Median duration of hospitalization, days	5.0	NA
Reported at least one serious ICANS event with hospitalization, no. (%)	2 (2.0)	0 (0.0)
Median duration of hospitalization, days	5.0	NA

Abbreviations: CRS, cytokine response syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome and associated neurologic events; NA, not applicable/available.

^aFever, hypotension, and fatigue were the most frequently reported serious adverse events in the 27 patients.

^bICANS in the DeLLphi-301 trial was defined as the occurrence of ICANS or an associated neurologic event identified on the basis of a broad search using 61 selected preferred terms from the Medical Dictionary for Regulatory Activities, version 26.1.

^cConfusion was the reported serious adverse event for both patients.

Neutropenia

Neutropenia is an identified risk for patients receiving tarlatamab.²⁶ In the DeLLphi-301 trial, treatment-emergent neutropenia was reported in 21 of 133 patients (16%). Based on 21 patients who had events, the median time to onset of neutropenia was 56 days (IQR, 30–86 days; Figure 1). Febrile neutropenia was reported in one of 133 patients (less than 1%). Neither neutropenia nor febrile neutropenia led to tarlatamab discontinuation. In the clinical trial setting, institution-specific protocols were suggested for the management of grade 1 or 2 neutropenia. For grade ≥ 3 neutropenia, treatment interruption was suggested until the severity decreased to grade 2 or lower. The use of granulocyte-colony-stimulating factor was permitted for the management of grade 3 neutropenia. Tarlatamab discontinuation was advised if an initial grade 3 nonfebrile neutropenia did not improve to grade 1 or lower within 3 weeks or if an initial grade 4 nonfebrile neutropenia lasted for >7 days or recurred at a lower dose level.

Liver enzyme elevations

An alanine aminotransferase (ALT) increase was observed in 15 patients (11.3%), and two patients (1.5%) experienced a grade 3 event. The median time to onset of ALT increase from the first tarlatamab dose was 29 days (IQR, 7–113 days). For the 14 patients (10.5%) who had increased aspartate aminotransferase (AST) levels, the median time to onset was 51 days (IQR, 3–196 days). One patient had

elevated aminotransferase and total bilirubin greater than two times the upper limit of normal and alkaline phosphatase less than two times the upper limit of normal. Elevated blood bilirubin was observed in four patients (3%). No patient reported tarlatamab discontinuation because of increased ALT or AST levels. The changes in liver enzyme and bilirubin levels were generally transient, with no evidence suggesting extensive hepatocellular damage. Documenting baseline levels of liver enzymes and bilirubin before starting tarlatamab and monitoring before each dose of tarlatamab and as clinically indicated was performed in the DeLLphi-301 trial.

Other TEAEs

Other AEs reported in DeLLphi-301 included decreased appetite, fatigue, anemia, and infections. Decreased appetite and fatigue are AEs that, if not appropriately monitored and managed, can negatively affect long-term patient experience. In DeLLphi-301, decreased appetite was reported in 48 of 133 patients (36%), and fatigue was reported in 32 of 133 patients (24%). Standard nonpharmacologic approaches, such as encouraging patients to undertake an optimal level of activity under the guidance of a health care provider, massage therapy, acupuncture, psychosocial interventions, nutrition consultations, and pharmacologic interventions, have been suggested for the management of fatigue in patients undergoing cancer treatment.²⁷ Anemia was observed in 40 patients (30%), with a median time to onset of 13.0 days (range, 1–275 days) from the first tarlatamab dose. (Figure 1).

TABLE 6 Immune effector cell-associated neurotoxicity syndrome grade, defining symptoms, management, and dose modification as used in the DeLLphi-301 trial.

ICANS grade ^a	Defining symptoms	Management	Dose modification
Grade 1	ICE score 7–9 ^c with no depressed level of consciousness	- Consider diagnostic work-up for alternative diagnosis - Supportive care	No treatment interruption needed
Grade 2	ICE score 3–6 ^c and/or mild somnolence awakening to voice	- Manage as for grade 1 - Dexamethasone^b 10 mg IV (can repeat every 6 hours) or methylprednisolone 1 mg/kg IV every 12 hours if symptoms worsen	No treatment interruption needed
Grade 3	ICE score 0–2 ^c ; 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	- Manage as for grade 2 - ICU care - Consider mechanical ventilation for airway protection - Dexamethasone^b 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 the patient has persistent grade ≥ 3 neurotoxicity	- Interrupt tarlatamab for at least 3 days and until the initial event improves to grade ≤ 1, then restart tarlatamab - If there is no improvement to grade ≤ 1 within 7 days or if grade 3 toxicity re-occurs within 7 days of re-initiation, permanently discontinue tarlatamab
Grade 4	ICE score 0 ^c (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 deep, focal motor weakness, such as hemiparesis or paraparesis; and/or diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, or papilledema, cranial nerve VI palsy, or Cushing's triad	- Manage as for grade 3 - ICU care - Consider mechanical ventilation for airway protection - High-dose corticosteroids^b - Consider repeat neuroimaging (CT or MRI) every 2–3 days if the patient has persistent grade ≥ 3 neurotoxicity - Treat convulsive status epilepticus according to institutional guidelines	Permanently discontinue tarlatamab

Note: ICANS in the DeLLphi-301 trial was defined as the occurrence of ICANS or an associated neurologic event identified on the basis of a broad search using 61 selected preferred terms from the Medical Dictionary for Regulatory Activities, version 26.0.

Abbreviations: CT, computed tomography; EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome and associated neurologic events; ICE, immune effector cell-associated encephalopathy; ICU, intensive care unit, IV, intravenous; MRI, magnetic resonance imaging.

^aBased on the American Society for Transplantation and Cellular Therapy consensus grading (2019).⁶

^bTaper steroids according to standard-of-care guidelines.

^cIf patient was arousable and an ICE assessment could be performed, they were evaluated on orientation, naming objects, following commands, writing, and attention (for additional details, see Table S5).

Among 57 patients with infections, the median time to onset was 37.0 days (range, 2–436 days). Grade ≥ 3 treatment-emergent infections, including opportunistic infections, occurred in 17 of 133 patients (13%). The most frequent grade ≥ 3 treatment-emergent infections were pneumonia ($n = 6$), respiratory tract infection ($n = 3$), device-related infection, and pneumonia aspiration ($n = 2$ each). Infections were managed using relevant institution-specific protocols. For all infections, the prescribing information recommends withholding tarlatamab until resolution or, in the case of a grade 3 infection (graded according to Common Terminology Criteria for Adverse Events, version 5.0 guidelines¹⁷), withholding tarlatamab until infection improved to grade 1 or lower.²⁸ Permanent

discontinuation of tarlatamab was recommended in the case of a grade 4 infection.²⁸

Considerations for patient management

Early identification of the signs and symptoms of AEs and an awareness of management practices may help health care providers optimize care for patients who are receiving tarlatamab. Thus patients in the DeLLphi-301 trial were monitored in a health care facility for 24–48 hours after the first two doses of tarlatamab. Investigators also took into consideration the ability to rapidly

transfer patients to an intensive care unit to manage higher grade CRS or ICANS events. After hospital discharge, patients were to be accompanied by a caregiver and remain within 1 hour of an appropriate health care setting for a total of 72 hours postinfusion after the first two tarlatamab doses. Other considerations identified by investigators that can aid in optimizing the management of CRS and ICANS are listed in Table 7. Health care providers educated patients and caregivers on recognizing the signs and symptoms of CRS and ICANS. They were taught to recognize CRS symptoms, such as fever, difficulty breathing or unusual shortness of breath, headache, chest pain, palpitations, persistent nausea or vomiting, chills, and/or myalgia, and were advised on the appropriate administration of acetaminophen. Patients and caregivers were also instructed on monitoring changes in vital signs (body temperature $\geq 38^{\circ}\text{C}$, blood pressure, oxygen saturation, and heart rate) for the early identification of AEs. When a patient living in a rural setting developed symptoms suggestive of CRS, the patient and caregiver were

instructed to treat with dexamethasone and visit the emergency room for further help.

Patients and caregivers were also taught to recognize neurologic symptoms that could be manifestations of ICANS, such as headache, dysgeusia, dizziness, insomnia, muscular weakness, ataxia, amnesia, confusion, disorientation, and lethargy. They were instructed to call or see their treating health care provider right away or go to the emergency room if they experienced any neurologic symptoms at any time during their treatment with tarlatamab. Patients were also advised to refrain from driving, operating heavy or potentially dangerous machinery, and engaging in hazardous occupations or activities until their neurologic symptoms resolved.

Patient or caregiver diaries with a descriptive record of symptoms, timing, and duration of AEs can assist health care providers with the management of AEs (Table 7). In addition, at one site, patients and caregivers were provided wallet cards with key contact information and asked to show the wallet card to health care providers.

TABLE 7 Investigator-suggested considerations for optimal management of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.^a

	To consider
Facilities and staff	• Infusion in specialized centers with a capacity for inpatient care • Rapid access to a dedicated intermediate/ICU bed during the period when the patient is at greatest risk of developing CRS (typically the first two doses of tarlatamab) • Adequate number of staff for postinfusion, vital sign monitoring^b
Education	• Educate patients on symptom recognition for CRS and ICANS. • Educate health care providers (physicians, nurses, staff at local emergency centers and ICUs) on T-cell engager-specific AE recognition and management. • Educate patients and caregivers on keeping a diary that provides a descriptive record of symptoms, timing, and duration of AEs.
Protocol	• Develop an institution-specific and drug-specific management protocol that can be readily accessed by all health care personnel involved in patient care. • Develop protocol for adapting premedication and postmedication doses and monitoring, depending on prior patient history of adverse events with the drug.
Medication	• In addition to protocol-mandated premedication, ready access to at least two doses of tocilizumab to treat grade ≥ 2 CRS quickly, if needed
Other considerations	• Start infusion as early in the morning as possible to allow for longer patient monitoring by the main day shift. • Development of a detailed handover protocol for the night-shift staff • Coordination with pharmacy for optimal drug delivery • Develop refined toxicity management protocols to define parameters for the outpatient setting similar to those used with CAR-T therapies. • Provide patients with key contact information.

Abbreviations: AEs, adverse events; CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome and associated neurologic events; ICU, intensive care unit.

^aAlthough not included in the DeLLphi-301 study protocol, some investigator-suggested considerations for the management of CRS and ICANS are listed. These considerations were based on personal clinical experience, and clinicians should use their own independent medical judgement for their individual patient's circumstances.

^bFor the frequency of postinfusion patient monitoring, see Table S9.

DISCUSSION

To date, the experience with chimeric antigen receptor T-cell therapies in hematologic malignancies has driven the management of CRS and ICANS. However, it is important to distinguish the safety profile of tarlatamab. In the DeLLphi-301 trial, CRS and ICANS were generally low-grade and manageable with standard supportive care that included acetaminophen, intravenous hydration, and/or glucocorticoids. CRS-associated fever usually occurred within hours of tarlatamab administration and was sometimes the only symptom before it resolved. Progression to higher-grade CRS generally took hours and, in most instances, was conservatively managed. ICANS occurred with a relatively low incidence, was low-grade, and was typically managed with corticosteroids. Although ICANS occurred more frequently in patients who had treated, stable brain metastases

in the DeLLphi-301 phase 2 trial, this correlation was not observed in the DeLLphi-300 phase 1 trial.^{29,30}

Additional AEs experienced by patients treated with tarlatamab include cytopenias, liver enzyme elevations and dysgeusia, which typically can be managed with standard of care (Figure 3).

CONCLUSIONS

Clinical trial experience indicates that tarlatamab has a manageable safety profile with a low discontinuation rate (3%) because of treatment-related AEs. Tarlatamab-associated AEs, including immune-related AEs like CRS and ICANS, were primarily grade 1 or 2 in severity, mostly occurred early during treatment (cycle 1), and generally could be managed with standard supportive care.

DeLLphi-301		
Adverse Events	Observations	Patient Management
 CRS	- CRS incidence = 53% - Grade 1 (fever) in 32% - Grade 2 (hypoxia and hypotension) in 20% - Grade 3 in < 1% - Primarily occurred following first or second dose - Median time to onset: 13.7 hours (IQR, 9.3 – 33.2)	- Sites monitored patients closely following first two doses - CRS was generally managed with supportive care including antipyretics (acetaminophen), IV hydration, and/or glucocorticoids - Sites were required to have corticosteroids and tocilizumab available onsite (or siltuximab if tocilizumab was not available)
 ICANS	- ICANS incidence = 10% - Events were Grade 1 or 2 - Median time to onset: 30 days (IQR, 13 – 47)	- ICANS symptoms included confusion, impaired attention, motor weakness/findings, dysgraphia, and increased tone - Grade 1 ICANS was managed with supportive care - Grade 2 was managed with steroid (eg, dexamethasone)
 Dysgeusia	- Dysgeusia incidence = 32% - Median time to onset: 34 days (IQR, 21 – 51)	- Investigators used previously published strategies for managing dysgeusia including: - Nutritional counseling by registered dietitian - Maintenance of good oral dental hygiene - Maintenance of adequate hydration (~ 1.5 – 2 L of water/day) - Periodic chewing of cardamom; inhaling smell of cloves and lemon ≥ 2x/day for ~15 seconds
 Neutropenia	- Neutropenia incidence = 16% - Median time to onset: 56 days (IQR, 30 – 86) - Febrile neutropenia in < 1% - Did not result in treatment discontinuation	- Institution-specific protocols were suggested for management of grade 1-2 neutropenia - For grade ≥ 3 neutropenia: - Use of granulocyte colony-stimulating factor (G-CSF) was permitted - Treatment interruption were considered until severity decreases to grade 2 or lower
 Elevated LFTs	- ALT increased incidence = 11% - Grade 3 in 1.5% - Median time to onset: 29 days (IQR, 7 – 113) - AST increased incidence = 11% - Median time to onset: 51 days (IQR, 3 – 196) - Generally transient with no evidence suggesting extensive hepatocellular damage - Did not result in treatment discontinuation	- Investigators documented baseline levels of liver enzymes and bilirubin prior to start of tarlatamab - LFTs were monitored with each tarlatamab dose and as clinically indicated

FIGURE 3 Common and adverse events of interest in the DeLLphi-301 trial. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome and associated neurologic events; IQR, interquartile range; IV, intravenous; LFTs, liver function tests.

Monitoring, detection, and appropriate management of AEs like CRS and ICANS will remain important for maintaining the continuity of care. Knowledge of other AEs, such as neutropenia, transient liver enzyme elevations, and dysgeusia, is also important to consider, especially during the long-term treatment of patients on tarlatamab. Continuous patient education by nurses and pharmacists may help with symptom monitoring and management and optimize long-term patient treatment experience.

AUTHOR CONTRIBUTIONS

Jacob M. Sands: Conceptualization; writing—review & editing; investigation. **Stéphane Champiat:** Conceptualization; investigation; writing—review & editing. **Horst-Dieter Hummel:** Conceptualization; investigation; writing—review & editing. **Kelly G. Paulson:** Conceptualization; investigation; writing—review & editing. **Hossein Borghaei:** Conceptualization; investigation; writing—review & editing. **Jean Bustamante Alvarez:** Conceptualization; investigation; writing—review & editing. **David P. Carbone:** Conceptualization; investigation; writing—review & editing. **Jennifer W. Carlisle:** Conceptualization; investigation; writing—review & editing. **Noura J. Choudhury:** Conceptualization; investigation; writing—review & editing. **Jeffrey M. Clarke:** Conceptualization; investigation; writing—review & editing. **Shirish M. Gadgil:** Conceptualization; investigation; writing—review & editing. **Hiroki Izumi:** Conceptualization; investigation; writing—review & editing. **Alejandro Navarro:** Conceptualization; investigation; writing—review & editing. **Sally C. M. Lau:** Conceptualization; investigation; writing—review & editing. **Philip E. Lammers:** Conceptualization; investigation; writing—review & editing. **Shuang Huang:** Conceptualization; methodology; validation; writing—review & editing; formal analysis; data curation. **Ali Hamidi:** Conceptualization; writing—review & editing; formal analysis; validation; methodology; data curation. **Sujoy Mukherjee:** Conceptualization; methodology; validation; writing—review & editing; formal analysis; data curation. **Taofeek K. Owonikoko:** Conceptualization; investigation; writing—review & editing.

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DATA AVAILABILITY STATEMENT

Qualified researchers may request data from Amgen clinical studies. Details are available at <https://www.amgen.com/datasharing>.

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