

Clinical Review of Tarlatamab-dlle

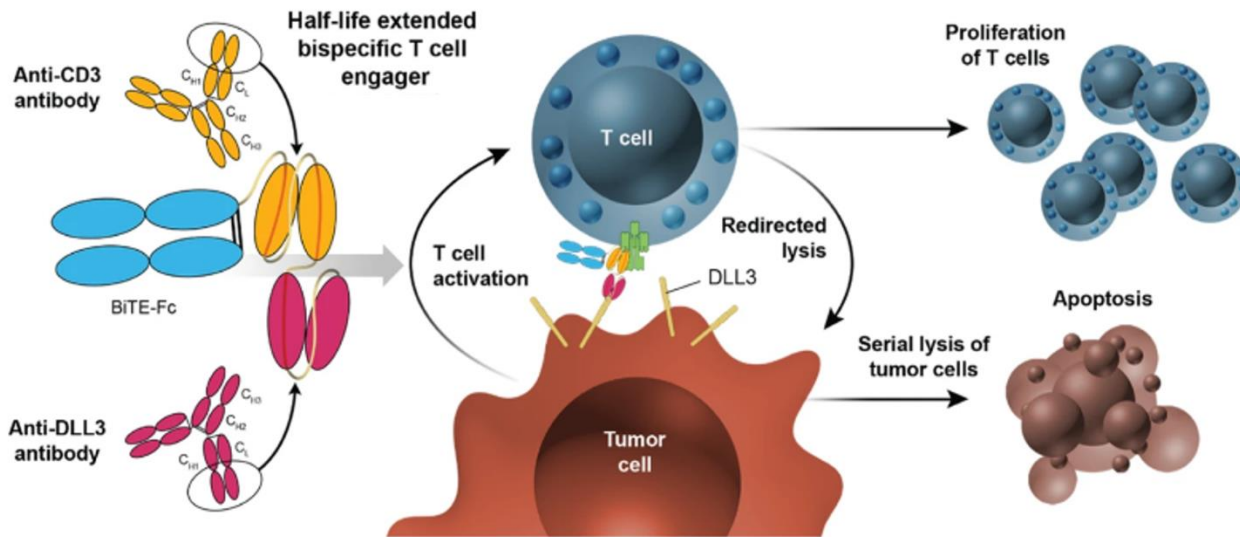
The First Bispecific T-Cell Engager (BiTE) Therapy for the Treatment of Extensive Stage Small-Cell Lung Cancer

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What is Tarlatamab-dlle?

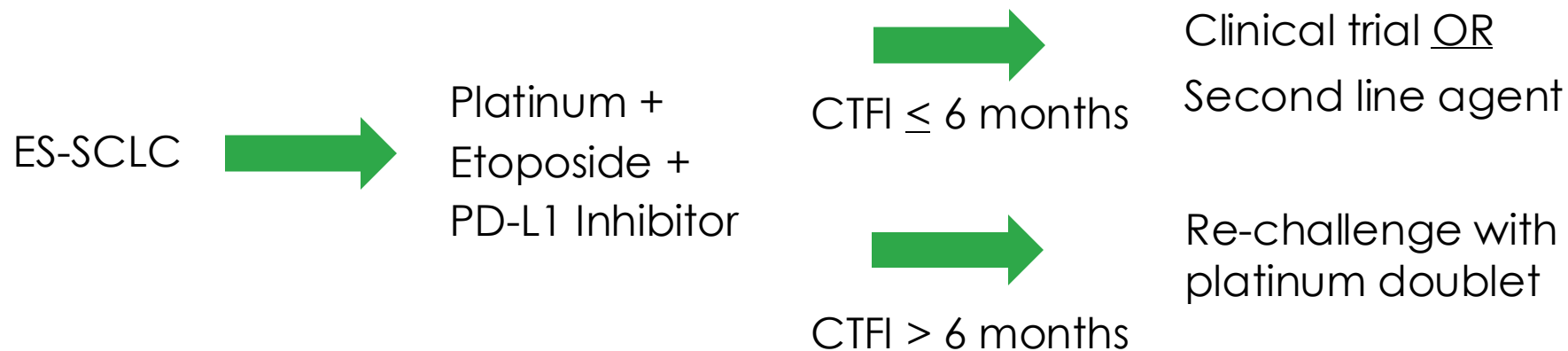


- Half-life extended (HLE) bispecific T cell engager (BiTE) targeting the DLL3 antigen while engaging patient's T cells through the CD3 antigen
- **DLL3:** Delta-like ligand 3
 - Inhibitory Notch pathway ligand
 - Highly upregulated in small cell lung cancer (SCLC)
 - DLL3 is expressed on the cell surface of more than 80% of SCLCs
 - Few normal cell types express DLL3
- First in class bispecific antibody directed at DLL3
 - Prior DLL3 targeting ADC, rovalpituzumab tesirine, proved to be unsuccessful



Small Cell Lung Cancer (SCLC)

- Accounts for 10-15% of lung cancers
 - Aggressive subtype
 - Rapid doubling, early metastatic growth
 - 5-year survival: 7%
 - **Limited stage:** disease confined to 1 hemithorax (30%)
 - **Extensive stage:** disease cannot be encompassed within a single radiotherapy field
- Extensive stage
 - Standard of care is combination systemic therapy with platinum + etoposide + PD-L1 inhibitor
 - Initial responses to therapy are very good, 60-70%
 - Resistance eventually develops
 - Median overall survival of 10-12 months after diagnosis



DeLLphi-301 Study

- Open-label
- International
- Consisted of 3 parts

Part 1: Dose Evaluation

Tarlatamab 10 mg*
D8, D15, Q2W thereafter
(n = 88)

Tarlatamab 100 mg*
D8, D15, Q2W thereafter
(n = 88)

*1 mg on D1.

Patients with ES-SCLC; ≥2 prior lines of tx, including platinum-based CT; treated, stable brain mets allowed; ECOG PS 0-1 (N = 222)

Part 2: Dose Expansion

Tarlatamab 10 mg*
D8, D15, Q2W thereafter
(n = 12)

Continued until a combined 100 pts. enrolled at selected dose

Part 3: Reduced Inpatient Monitoring Period

Tarlatamab 10 mg*
D8, D15, Q2W thereafter
(n = 34)

During cycle 1, reduced from 48 hours to 24 hours

Pre- & post-medication:

Dexamethasone 8 mg IV – Days 1 & 8 of cycle 1 only, prior to tarlatamab dose
Normal saline 1 liter over 4-5 hours – Immediately after all doses in cycle 1



Patients

Inclusion

- Adults aged 18 years or older
- Relapsed or refractory small cell lung cancer following one platinum-based regimen and ≥ 1 other line of therapy
 - Platinum-based rechallenge considered to be a 2nd line of therapy
- ECOG PS 0 or 1 with minimum life expectancy of 12 weeks
- Measurable lesions per RECIST 1.1
- Stable, treated brain metastases allowed
 - Required to be off steroids & asymptomatic for at least 7 days
- Adequate organ function

Exclusion

- Untreated or symptomatic brain metastases and leptomeningeal disease
- Evidence of interstitial lung disease or pneumonitis
- Unresolved toxicity from prior therapy
- History of other malignancy within the past 2 years (some exceptions allowed)
- MI or symptomatic CHF within 12 months
- History of arterial thrombosis within 12 months
- Presence of fungal, bacterial, viral, or other infection requiring IV/PO antibiotics within 7 days
- History or evidence of severe acute respiratory syndrome SARS-CoV-2 infection; no acute symptoms of COVID-19 within 14 days



Notable Baseline Demographics

	Tarlatamab 10 mg		Tarlatamab 100 mg
	Parts 1 and 2 (N=100)	Part 3 (N=34)	Part 1 (N=88)
Median age (years)	64.0	65.5	62.0
Sex			
Male	72 (72%)	24 (71%)	62 (70%)
Race/Ethnic Group			
Asian	41 (41%)	2 (6%)	26 (41%)
Black	0 (0%)	1 (3%)	0 (0%)
White	58 (58%)	31 (91%)	49 (56%)
Smoking History			
Never	8 (8%)	1 (3%)	5 (6%)
Current	19 (19%)	5 (15%)	10 (11%)
Former	73 (73%)	28 (82%)	73 (83%)
Brain Metastases Present	23 (23%)	4 (12%)	32 (36%)
Median lines of prev. tx	2.0	2.0	2.0
DLL3 Expression	80/83 (96%)	NA	71/74 (96%)



Efficacy

Includes all 176 patients enrolled in part 1 and 12 patients enrolled in part 2. Patients from part 3 were considered immature at time of analysis.

Median follow-up: 10.6 months

Objective Response Rate (ORR, by BICR):

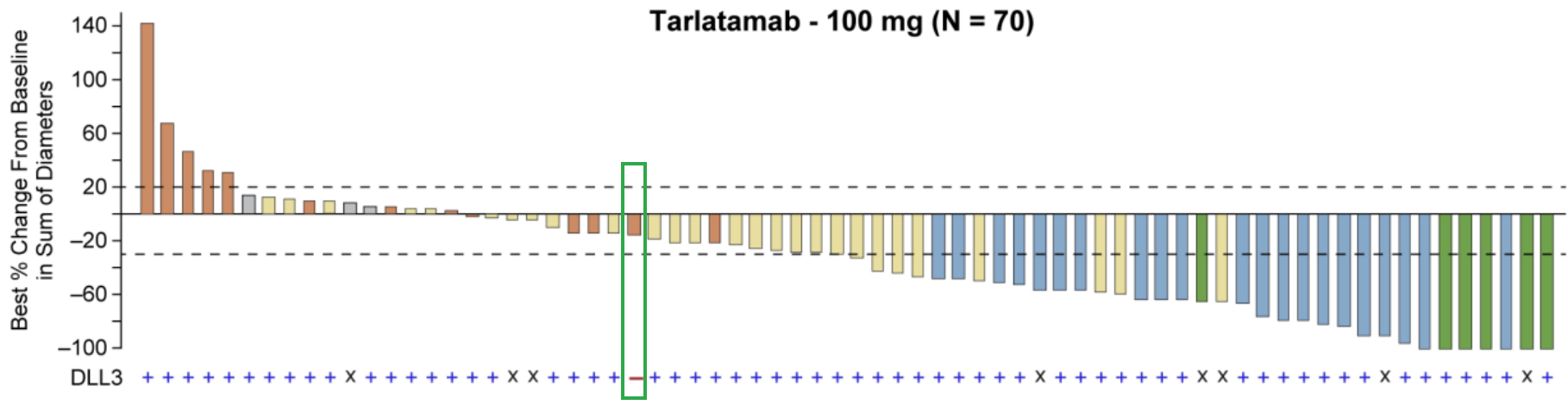
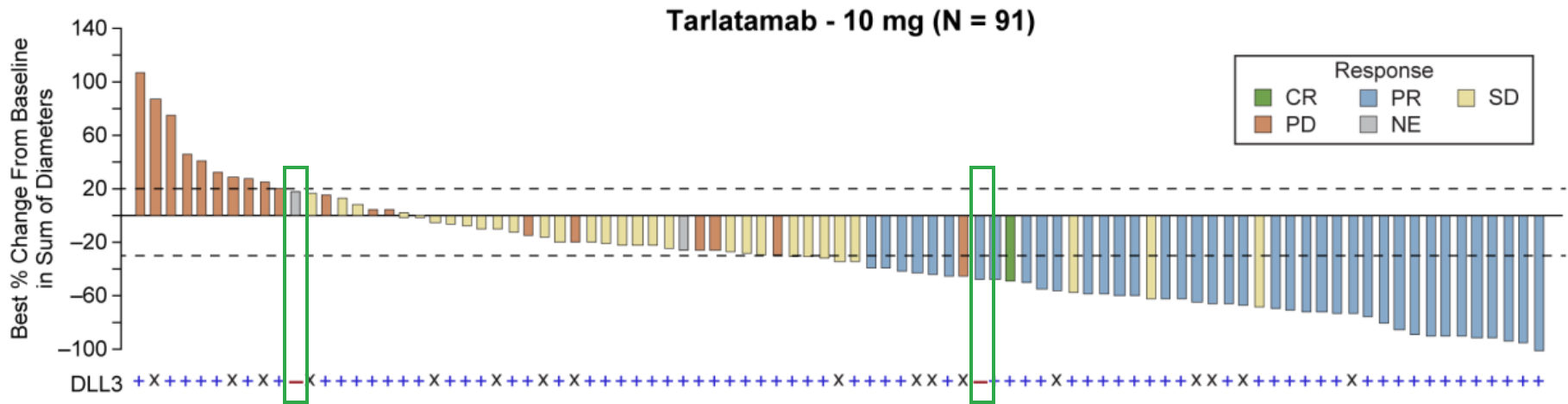
- 10 mg group: 40%
- 100 mg group: 32%

Outcome	Tarlatamab 10 mg (N=100)	Tarlatamab 100 mg (N=88)
Complete response	1%	8%
Partial response	39%	24%
Stable disease	30%	31%
Median duration of response (DoR) - months	NE (5.9 – NE)	NE (6.6 – NE)
Observed DoR \geq 6 months	23/40 (58%)	17/28 (61%)

Responses were seen in patients with tumor samples that were positive, negative, and not evaluable for DLL3 expression



Antitumor Activity



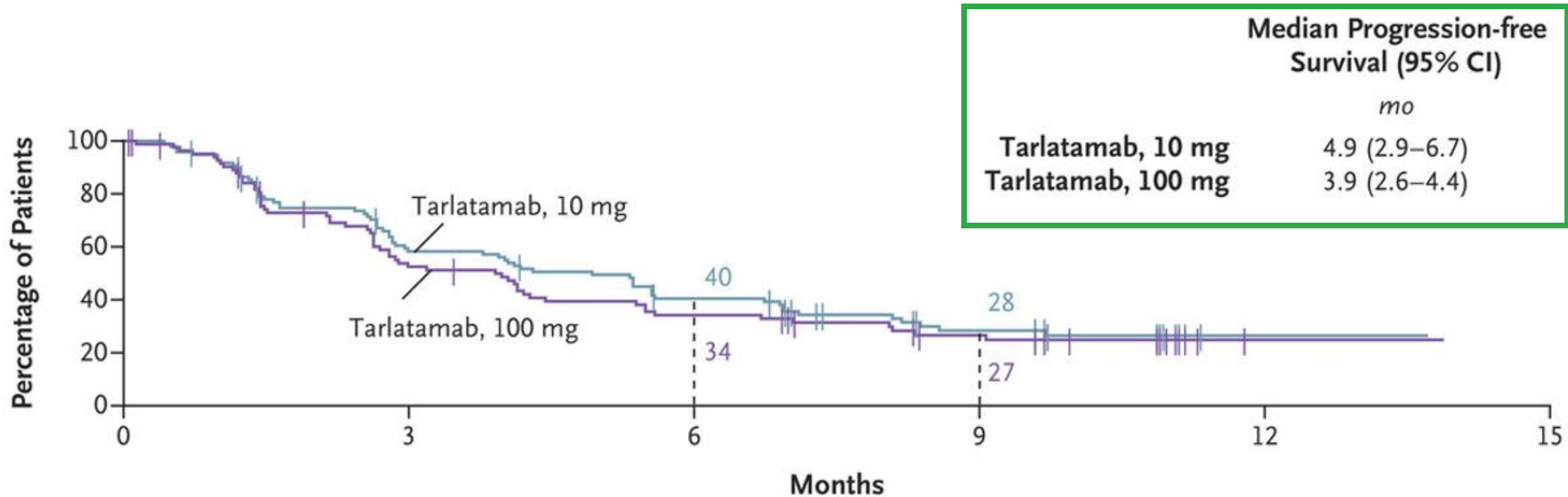
+ : DLL3 detectable
 - : DLL3 undetectable
 X : Not evaluable/unavailable

- Responses were seen in patients with tumor samples that were positive, negative, and not evaluable for DLL3 expression



Efficacy

Progression-free Survival (PFS)



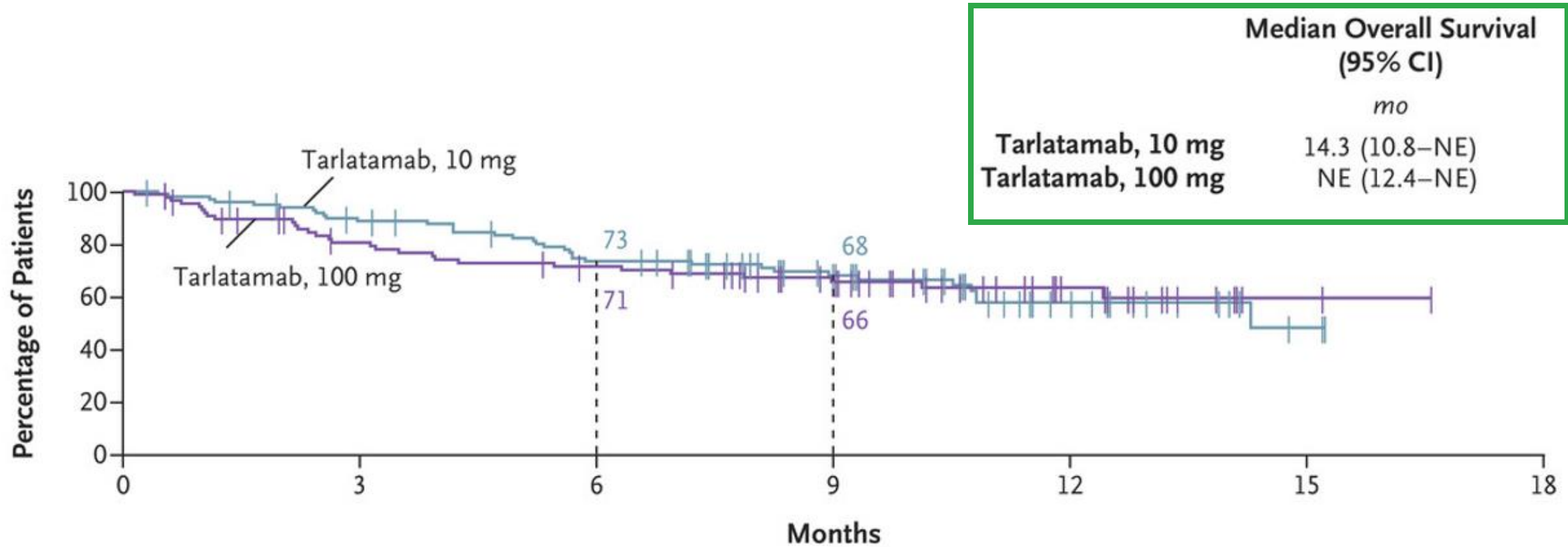
No. at Risk

	0	3	6	9	12	15
Tarlatamab, 10 mg	100	53	35	18	2	0
Tarlatamab, 100 mg	88	41	26	15	3	0



Efficacy

Overall Survival (OS)



No. at Risk

	0	3	6	9	12	15	18
Tarlatamab, 10 mg	100	84	67	44	17	3	0
Tarlatamab, 100 mg	88	62	53	39	16	2	0



Safety – CRS, ICANS, Neutropenia

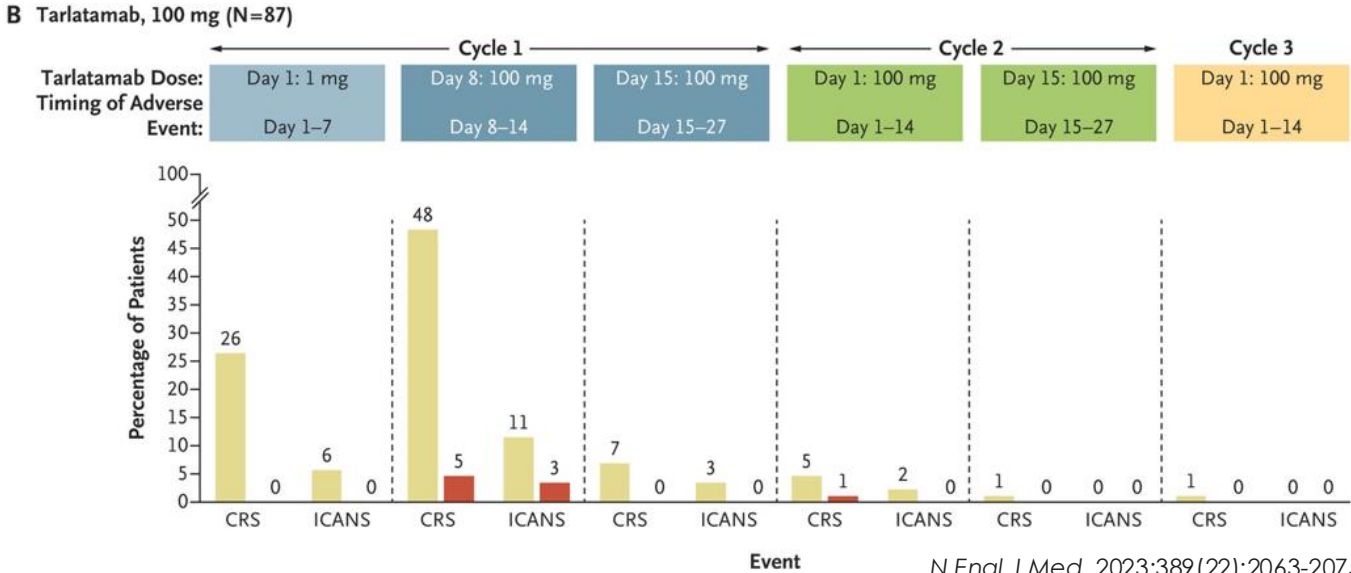
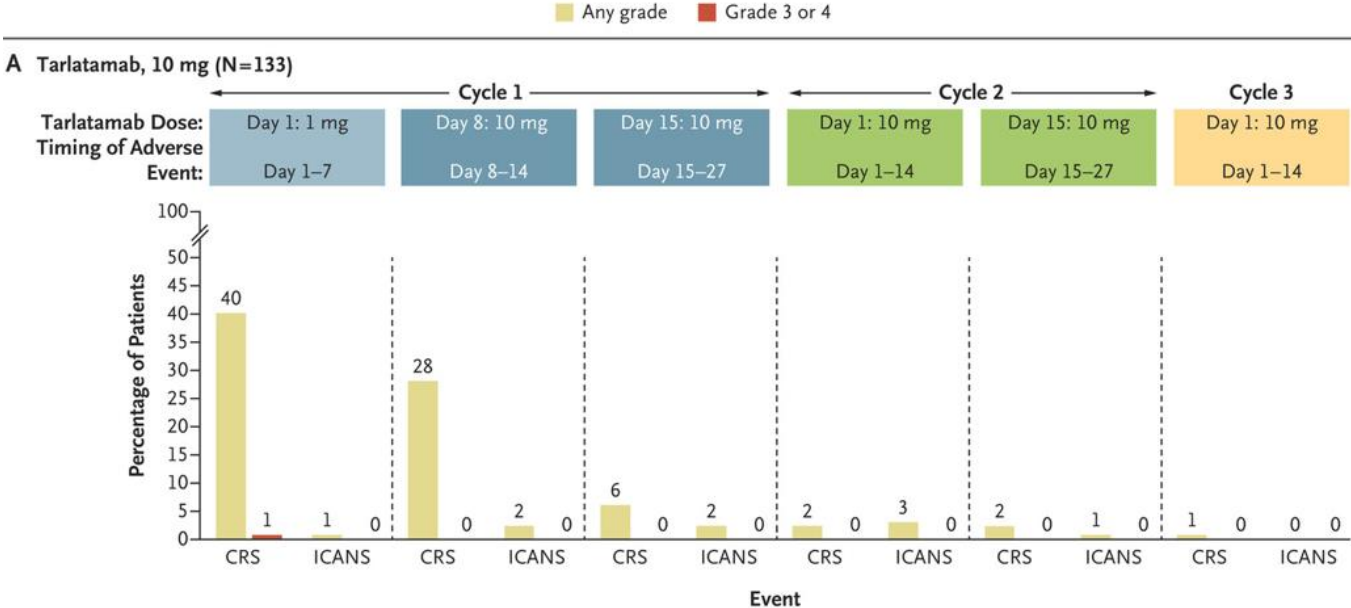
Adverse Events	Tarlataamab, 10 mg		Tarlataamab, 100 mg	
	Parts 1 & 2 (N=99)	Part 3 (N=34)	Parts 1,2 & 3 (N=133)	
			Part 1 (N=87)	
Any grade	96 (97%)	34 (100%)	130 (98%)	87 (100%)
Grade ≥ 3	57 (58%)	22 (65%)	79 (59%)	56 (64%)
Grade ≥ 4	16 (16%)	7 (21%)	23 (17%)	13 (15%)
Fatal	3 (3%)	4 (12%)	7 (5%)	5 (6%)
Leading to interruption, reduction, or both	31 (31%)	5 (15%)	36 (27%)	39 (45%)
Leading to discontinuation	7 (7%)	3 (9%)	10 (8%)	6 (7%)
Cytokine Release Syndrome	49 (49%)	19 (56%)	68 (51%)	53 (61%)
Grade ≥ 3	0	1 (3%)	1 (1%)	5 (6%)
ICANS/Neurologic Events	7 (7%)	4 (12%)	11 (8%)	24 (28%)
Grade ≥ 3 Severity	0 (0%)	0 (0%)	0 (0%)	4 (5%)
Neutropenia	18 (18%)	5 (15%)	23 (17%)	14 (16%)
Grade ≥ 3 Severity	6 (6%)	2 (6%)	8 (6%)	9 (10%)



CRS Onset and Interventions

Cytokine Release Syndrome (CRS)

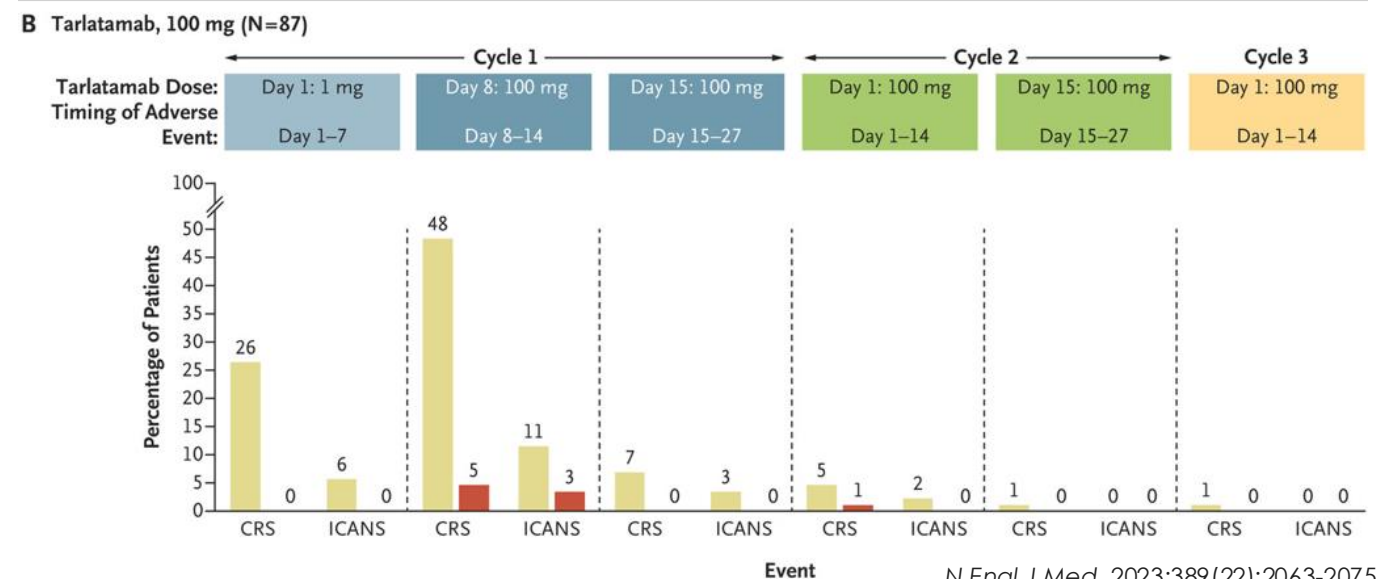
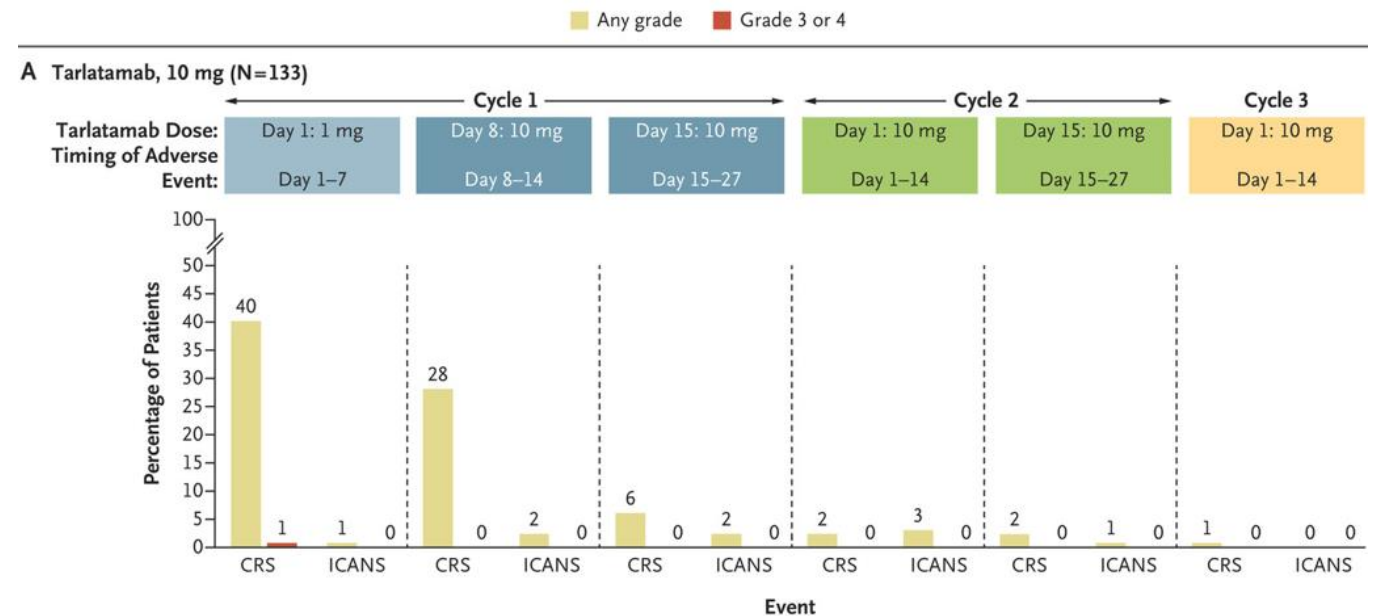
- Onset from last tarlatamab dose: 13.1 hrs
 - IQR: 7.8-27.4 hrs
- Duration: 4 days
- Interventions
 - Tocilizumab: 16 (7.3%)
 - Vasopressor use: 2 (0.9%)
 - IV hydration: 17 (7.7%)
 - Supplemental oxygen: 19 (8.6%)



ICANS Onset and Presentation

Immune-effector Cell-associated Neurotoxicity Syndrome (ICANS)

- Onset (median): 5 days
- Time to resolution (median): 6.5 days
- Common signs/symptoms: confusion, impaired attention, tremor, motor findings, weakness
- Leading to interruption/reduction:
 - 10 mg group: 1 (1%)
 - 100 mg group: 5 (6%)
- Leading to discontinuation:
 - 1 patient in each dose group



DeLLphi-301 Conclusion

- Tarlatamab exhibited durable antitumor activity
- 10-mg dose has more favorable benefit-to-risk profile than the 100-mg dose
- Objective response of 40% far exceeds the historical control benchmark of 15%
- CRS most often occurred after 1st or 2nd dose & predominantly grade 1 or 2 severity
- Lack of standard-of-care comparator is one limitation of the trial

FDA Approval

Accelerated approval granted on May 16th, 2024 for extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based therapy.

- Based on overall response rate and duration of responses
- Continued approval contingent upon verification of clinical benefit
- The 10-mg dose was selected for commercial use and for future clinical trials



NCCN Small Cell Lung Cancer Guideline

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2) ^f Consider dose reduction or growth factor support for patients with PS 2.	
CHEMOTHERAPY-FREE INTERVAL (CTFI) >6 MONTHS	
Preferred Regimens	<ul style="list-style-type: none"> • Clinical trial enrollment • Re-treatment with platinum-based doublet^{g,34,35,37-39}
Other Recommended Regimens	<ul style="list-style-type: none"> • Lurbinectedin^{17,36} • Topotecan oral (PO) or intravenous (IV)^{14-16,28} • Irinotecan^{h,21,28} • Tarlatamab-dlle^{i,47}
CTFI ≤6 MONTHS	
Preferred Regimens	<ul style="list-style-type: none"> • Clinical trial enrollment • Lurbinectedin^{17,36} • Topotecan oral (PO) or intravenous (IV)^{14-16,28,37} • Irinotecan^{h,21,28} • Tarlatamab-dlle^{i,47} • Re-treatment with platinum-based doublet may be considered for CTFI 3–6 months^{g,37,38,39}
Other Recommended Regimens	<ul style="list-style-type: none"> • Nivolumab or pembrolizumab (if not previously treated with an ICI)^{b, 29,30,31,32,33} • Paclitaxel^{18,19} • Temozolomide^{22,23} • Cyclophosphamide/doxorubicin/vincristine (CAV)¹⁴ • Docetaxel²⁰ • Gemcitabine^{26,27,40} • Oral etoposide^{24,25}

Tarlatamab ORR: 40%

Lurbinectedin ORR: 35%

Topotecan ORR: ~7-25%



Dosing & Administration

28 day cycle	Pre-medication	Tarlatamab Dose	Post-hydration	Post-Infusion Monitoring*
C1D1	Dexamethasone 8 mg IV (or equivalent)	1 mg IV	Normal saline 1 liter over 4-5 hrs immediately following infusion	22-24 hrs
C1D8		10 mg IV		22-24 hrs
C1D15		Not required		10 mg IV

28 day cycle	Pre-medication	Tarlatamab Dose	Post-hydration	Post-Infusion Monitoring*
C2 D1,15	Not required	10 mg IV	Not required	6-8 hrs
C3-4 D1,15		10 mg IV		3-4 hrs
C5 + D1,15		10 mg IV		2 hrs

*In an appropriate healthcare setting

Re-start following delays

Last Dose	Time Elapsed	Action
1 mg C1D1	≤ 14 days	10 mg then resume with planned schedule
	> 14 days	Step-up dose 1 mg, if tolerated increase to 10 mg 1 week after
10 mg C1D8	≤ 21 days	10 mg then resume with planned schedule
	> 21 days	Step-up dose 1 mg, if tolerated then increase to 10 mg 1 week after
10 mg C1D15 and Subsequent Q2W Cycles	≤ 28 days	10 mg then resume with planned schedule
	> 28 days	Step-up dose 1 mg, if tolerated increase to 10 mg 1 week later



Monitoring

- CBC w/differential, liver enzymes and bilirubin:
 - Prior to treatment, prior to each dose, and as clinically indicated
- Post-infusion monitoring period (*as described in previous slide*)
 - If grade ≥ 2 CRS, ICANS, neurotoxicity develops, extended monitoring time may be necessary
 - Grade ≥ 2 CRS should be monitored with continuous cardiac telemetry and pulse oximetry; severe or life-threatening CRS requires intensive monitoring (eg, ICU)
- Signs/symptoms of CRS & ICANS
- Hepatitis B virus (HBV) screening



Drug-drug Interactions

Transient release of cytokines 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

- Monitor therapy
- Medications with narrow therapeutic index



Warnings

- Cytokine release syndrome (CRS)
- Neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS)
- Cytopenias
- Infections
- Hepatotoxicity
- Hypersensitivity
- Embryo-fetal toxicity



Cytokine Release Syndrome

- An uncontrolled systemic inflammatory response with elevated levels of pro-inflammatory cytokines, primarily IL-6, triggered by T cell activation
- Symptoms may range from mild flu-like symptoms to severe & fatal multi-organ failure
 - **Common CRS signs:** Fever, hypotension, tachycardia, hypoxia, chills
 - **Cardiac:** Tachycardias, arrhythmias, heart block, impaired LVEF
 - **Respiratory:** Dyspnea, tachypnea, hypoxia, pleural effusion, pulmonary edema
 - **Gastrointestinal:** Nausea, vomiting, anorexia, diarrhea
 - **Hepatic:** Elevated AST/ALT, hyperbilirubinemia
 - **Renal:** Decreased urine output, increased serum creatinine, AKI
 - **Dermatological:** Acneiform or maculopapular rash
 - **Coagulopathy:** Disseminated intravascular coagulation (DIC), prolonged PT/PTT, low fibrinogen, bleeding
- Grading of CRS follows the ASTCT Consensus Grading Scale for CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
With				
Hypotension	None	Not requiring vasopressors	Requiring vasopressors +/- vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation, mechanical ventilation)



Management of CRS

Grading	Definition	Dose Modification	Management Strategy
Grade 1	Symptoms require symptomatic treatment only (eg, fever \geq 100.4 Fahrenheit without hypotension/hypoxia)	Withhold until event resolves, resume at next scheduled dose	Supportive care (eg, acetaminophen for fever)
Grade 2	Symptoms require and respond to moderate intervention Fever \geq 100.4 Fahrenheit Hypotension responsive to fluids Hypoxia requiring low-flow nasal cannula or blow-by	Withhold until event resolves, resume at next scheduled dose	<ul style="list-style-type: none"> • Recommend hospitalization for 22-24 hrs with cardiac telemetry & pulse oximetry • Administer symptomatic tx (eg, acetaminophen for fever) • Supplemental O2 and IV fluids • Consider dexamethasone 8 mg IV • Consider tocilizumab When resuming, monitor pts. for 22-24 hours
Grade 3	Severe symptoms defined as temperature \geq 100.4 with: Hemodynamic instability requiring a vasopressor or Worsening hypoxia/respiratory distress requiring high-flow nasal cannula (>6 L/min oxygen) or face mask	Withhold until event resolves, resume at next scheduled dose Recurrent: Permanently discontinue	In addition to G2 interventions <ul style="list-style-type: none"> • Intensive monitoring • Administer dexamethasone 8 mg IV • Recommend tocilizumab • Vasopressor support as needed • High flow O2 as needed • Prior to next dose, administer concomitant medications as done for cycle 1 When resuming, monitor pts. for 22-24 hours
Grade 4	Life-threatening symptoms defined as temperature \geq 100.4 Fahrenheit with: Hemodynamic instability requiring multiple vasopressors Worsening hypoxia/respiratory distress despite oxygen administration requiring positive pressure	Permanently discontinue	<ul style="list-style-type: none"> • ICU care • Per G3 treatment • Recommend tocilizumab

Immune Effector Cell-Associated Neurotoxicity Syndrome

- Pathophysiology poorly understood; models have implicated endothelial cell activation and disruption of the blood-brain barrier resulting in direct neuronal cell injury in addition to a role for various pro-inflammatory cytokines
- Typically manifests as a toxic encephalopathy and starts with word-finding difficulty, confusion, dysphasia, aphasia, impaired fine motor skills and somnolence
- May present concurrently with or after CRS
- At first sign of neurotoxicity, withhold tarlatamab and consider neurology evaluation

Immune Effector Cell-Associated Encephalopathy (ICE) Score	Points
Orientation: orientation to year, month, city, hospital	4
Naming: ability to name 3 objects (e.g., point to clock, pen, button)	3
Following your commands: ability to follow simple commands (e.g., "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1
Writing: ability to write a standard sentence (e.g., "Our national bird is the bald eagle")	1
Attention: ability to count backwards from 100 by 10	1



Management of ICANS

Grading	ICE Score/Symptoms	Dose Modification	Management Strategy
Grade 1	7-9 with no depressed level of consciousness	Withhold until event resolves, resume at next scheduled dose	Supportive care
Grade 2	3-6 and/or mild somnolence awaking to voice	Withhold until event resolves, resume at next scheduled dose	<ul style="list-style-type: none"> • Supportive care • Dexamethasone 10 mg IV, may repeat every 6 hrs or methylprednisolone 1 mg/kg every 12 hrs • Monitor neurologic symptoms and consider neurology consultation • Monitor for 22-24 hrs following next dose
Grade 3	0-2 and/or: <ul style="list-style-type: none"> • Depressed level of consciousness awakening only to tactile stimulus • Any clinical seizure, focal or generalized, that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention • Focal or local edema on neuroimaging 	Withhold until ICANS resolves then resume at next scheduled dose <ul style="list-style-type: none"> • No improvement to grade \leq 1 within 7 days or G3 reoccurs within 7 days of re-initiation, permanently discontinue • Recurrent: Permanently discontinue 	In addition to G2 interventions <ul style="list-style-type: none"> • Recommend intensive monitoring • Consider mechanical ventilation • Dexamethasone 10 mg IV, may repeat every 6 hrs or methylprednisolone 1 mg/kg every 12 hrs • Repeat neuroimaging every 2-3 days if persistent G3+ neurotoxicity • Monitor for 22-24 hrs following next dose
Grade 4	Score of 0 (patient is unarousable and unable to perform ICE) and/or: <ul style="list-style-type: none"> • Stupor/coma • Life-threatening prolonged seizure (> 5 minutes) • Diffuse cerebral edema, decerebrate or decorticate posturing or papilledema, cranial nerve VI palsy, or Cushing's triad 	Permanently discontinue	<ul style="list-style-type: none"> • ICU care • Consider mechanical ventilation • High-dose corticosteroids • Repeat neuroimaging every 2-3 days if persistent G3+ neurotoxicity



Additional Adverse Event Management

Adverse Event	Severity	Dose Modification
Cytopenias	Grade 3/4 Neutropenia	Withhold until recovery to Grade ≤ 2 Consider administration of GCSF Permanently discontinue if recovery to Grade ≤ 2 does not occur within 3 weeks
	Recurrent Grade 4 Neutropenia	Permanently discontinue
	Febrile Neutropenia	Withhold until neutropenia recovers to Grade ≤ 2 and fever resolves
	Hemoglobin < 8 mg/dL	Withhold until hemoglobin is ≥ 8 g/dL
	Grade 3/4 Decreased Platelet Count	Withhold 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
Infection	All grades	Withhold in the step-up dose phase until infection resolves
	Grade 3	Withhold during the treatment phase until infection improves to Grade ≤ 1
	Grade 4	Permanently discontinue
Hepatotoxicity	Grade 3 Increased ALT/AST or bilirubin	Withhold until adverse event improves to Grade ≤ 1
	Grade 4 Increased ALT/AST or bilirubin	Permanently discontinue
	ALT/AST > 3 x ULN w/ total bilirubin > 2 x ULN in absence of other causes	Permanently discontinue



Patient Identification

- Alerts within electronic medical record notifying that patient is recent recipient of tarlatamab and should be monitored for associated toxicities
- Wallet card from manufacturer

(tarlatamab-dlle) WALLET CARD

THIS PATIENT HAS RECEIVED (FOR HCP)

Patient name

Date & time of first infusion

Provider name

Office phone

It is recommended that you carry this card with you at all times and show it to any healthcare provider involved in your care.

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

For more information,
visit
or scan the QR code here



Please see the full [Prescribing Information](#),
including **BOXED WARNINGS**, and Medication Guide.



Conclusion

- Tarlatamab-dlle represents a new therapeutic approach for patients with ES-SCLC who have progressed on prior therapies such as immunotherapy + chemotherapy
- Tarlatamab-dlle potentially offers improved response rate and duration of responses
- Monitoring and management plans should be standardized and implemented for common and potentially serious toxicities such as CRS, ICANS, and cytopenias
- Future studies examining combinations with other therapies and in direct comparison with previous standard-of-care options still needed



Thank You.

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