Tarlatamab Protocol

Tarlatamab is a bispecific delta-like ligand 3 (DLL3)-directed CD3 T cell engager indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

Eligibility for treatment

Age >18
Histologically or cytologically confirmed extensive stage SCLC with disease progression on or after platinum based SACT
Performance status ECOG 0-1
Presence of untreated or symptomatic central nervous system (CNS) metastases, leptomeningeal disease, or cord compression is a contraindication to treatment
Have no history of arrhythmia or significant heart disease or other comorbidity that could make fluid replacement for treatment of cytokine release syndrome (CRS) or Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) difficult- consider ECHO if concerns.
Have reasonable bone marrow, kidney and liver function (as per protocol)
Patients should not have evidence of interstitial lung disease or non infectious pneumonitis

Investigations– pre first cycle

Standard pre-SACT tests
Baseline ECG
Consider echo particularly with patients with history of CV disease

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), Bone, Magnesium, random glucose, clotting

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer must be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 60 mL/min
Bilirubin	≤ 1.0 x ULN
AST	< 1.5 x ULN

Dosage and administration

Step-up Dosing Schedule (Cycle 1):
Administer according to the step-up dosing schedule in Table 1 to reduce the incidence and severity of CRS.
Pre-medications:
Cycle 1 Day 1 and Day 8:
8mg dexamethasone 1 hour prior to infusion

Infusion Process (Cycle 1, Day 1 and Day 8)
Administer Tarlatamab as a 1-hour intravenous infusion (250ml) at a constant flow rate via an infusion pump.
Ensure patients are well-hydrated before administration.
Administer 1 litre of normal saline over 2-4 hours pre-infusion.

Post-Treatment Hydration:
On Days 1, 8, and 15 (Cycle 1), administer 1 litre of normal saline over 4 hours immediately after the dose to aid recovery and reduce side effects.

Patient Monitoring and Discharge:
Due to the risk of CRS and ICANS (Immune Cell-Associated Neurotoxicity Syndrome), treatment should be given inpatient.

Monitoring for Cycle 1:
Monitor the patient for 24 hours post-infusion on Cycle 1 Day 1 and Cycle 1 Day 8.
Recommend that patients remain within 1 hour of a healthcare facility for a total of 48 hours after the start of the infusion.
If this is not feasible, patients should remain as inpatients.

Discharge:
A senior decision maker (ST3 and above) should assess patient suitability for discharge after each infusion.

Subsequent Cycles:
For subsequent doses (after Cycle 1), inpatient monitoring should last 6-8 hours post-infusion.
The senior decision maker should again determine patient readiness for discharge.

Laboratory Tests Prior to Each Dose:
Evaluate FBC, U+E (including creatinine), LFT (including AST), Bone, Magnesium, random glucose and clotting factor before each dose to ensure the patient is fit for the next infusion.
Conduct these evaluations as clinically indicated and follow the predefined administration limits.

Table 1: Recommended Dosage and Schedule of Tarlatamab (from SPC)

Dosing Schedule	Day	Dose	Administration instructions	Recommended Monitoring
Step Up Dosing Schedule Cycle 1	Day 1	Step-up dose 1mg[a]	Administer Tarlatamab as a 1-hour intravenous infusion in an appropriate healthcare setting.	Monitor patients from the start of the Tarlatamab infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 as an inpatient. Recommend that patients remain within 1-hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with Tarlatamab, accompanied by a caregiver.
	Day 8	10mg[a]		
	Day 15	10mg[a]		Observe patients for 6-8 hours post Tarlatamab infusion[b]
Cycle 2	Day 1 and 15	10mg		Observe patients for 6-8 hours post Tarlatamab infusion[b]
Cycle 3 and 4	Day 1 and 15	10mg		Observe patients for 3-4 hours post Tarlatamab infusion[b]
Cycle 5 and subsequent infusions	Day 1 and 15	10mg		Observe patients for 2 hours post Tarlatamab infusion[b]

[a] Administer recommended concomitant medications Cycle 1 Day 1 and Day 8 8mg dexamethasone 1 hour prior to infusion. Post treatment on days 1, 8 and 15 give 1 litre normal saline over 4 hours immediately after dose.

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

Monitoring Requirements

Extended Monitoring:

- **Vital Signs**: Patients require extended monitoring with **vital signs recorded every 2 hours** during and after infusion.
- **Admission**: Patients will be **admitted overnight** for monitoring during dosing.
- **Discretion of Extended Monitoring**: The need for any further extended monitoring will be determined at the discretion of the treating physician based on the patient's history and tolerance of the initial doses.

Day of Admission Protocol:

Preparation:

Ensure this protocol is printed and available at the patient's bedside for easy access, along with the **CRS management protocol**.

Team Awareness:

Notify the following teams of the patient's admission:

- Oncology registrar and consultant on call.
- Critical care outreach team.
- Clinical night team and medical team on call.

Drug Availability:

Confirm that the ward has sufficient stock of:

- **IV methylprednisolone** (in case of infusion reactions).
- **Tocilizumab** (available in the pharmacy).

Ward Prescriptions:

Ensure the following medications are prescribed and available on the ward:

- **Chlorphenamine (Piriton)**: 10mg IV qds/prn.
- **Hydroxyzine hydrochloride (Atarax)**: 25mg PO qds/prn.
- **Paracetamol**: 1g PO/IV qds/prn.
- **Ibuprofen**: 400mg PO tds/prn (if no contraindications).
- **Epimax/E45 cream**: PRN for skin irritation.
- **Hydrocortisone**: 200mg IV in case of infusion reaction.

Physical Examination and Monitoring:

- Perform a full physical examination before each treatment to ensure the patient is well enough to proceed, including an assessment of fluid status.
- Temperature and Blood Pressure: Pay particular attention to the patient's temperature and blood pressure.
- CRS Monitoring: A rise in body temperature, typically 3-4 hours post-infusion, should trigger suspicion of CRS.

Pre-Treatment Blood Pressure Protocol:

- Seat the patient for at least 20 minutes before measuring blood pressure.
- Measure BP twice, 5 minutes apart, using the same upper limb if possible.
- Calculate the average systolic BP by adding both readings and dividing by two.
- Record the baseline systolic BP clearly and legibly for future reference.

Side effects and management

The most common adverse reactions (≥20%) are cytokine release syndrome, fatigue, pyrexia, dysgeusia, decreased appetite, musculoskeletal pain, constipation, anaemia and nausea.
The most common Grade 3 or 4 laboratory abnormalities (≥2%) are decreased lymphocytes, decreased sodium, increased uric acid, decreased total neutrophils, decreased haemoglobin, increased activated partial thromboplastin time, decreased potassium, increased aspartate aminotransferase, decreased white blood cells, decreased platelets, and increased alanine aminotransferase.

Cytokine release Syndrome (CRS)

Cytokine storm is a predictable side effect of treatment recorded in 55% (any grade) and 1.6% (grade 3/4) patients in the DELPHI 300 and 301 studies.

Management of CRS:

- **Symptoms**: CRS can cause significant blood pressure changes, febrile reactions, and may require interventions such as fluid resuscitation, vasopressors, inotropes, supplemental oxygen (O2), or assisted ventilation in rare cases.
- **Resolution**: Symptoms typically resolve after **3 days**.
- **Patient Counselling**: Patients should be counselled about the risk and signs of CRS, including:
    - **Pyrexia**, **hypotension**, **fatigue**, **tachycardia**, **headache**, **hypoxia**, **nausea**, and **vomiting**.
    - Patients should immediately contact the **24-hour SACT helpline** if they experience any of these symptoms.

Grading of severity is based on the American Society for Transplantation and Cellular Therapy (ASTCT).

Grade	Fever	with Hypotension	and/or Hypoxia
1	≥ 38.0 °C	None	None
2	≥ 38.0 °C	Not requiring vasopressors	Requiring oxygen delivered by low-flow nasal cannula (≤ 6 L/min)
3	≥ 38.0 °C	Requiring a vasopressor with or without vasopressin	Requiring oxygen delivered by high-flow nasal cannula (> 6L/min), facemask, nonrebreather mask, or Venturi mask
4	≥ 38.0 °C	Requiring multiple vasopressors (excluding vasopressin)	Requiring oxygen delivered by positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Management Protocol for CRS:

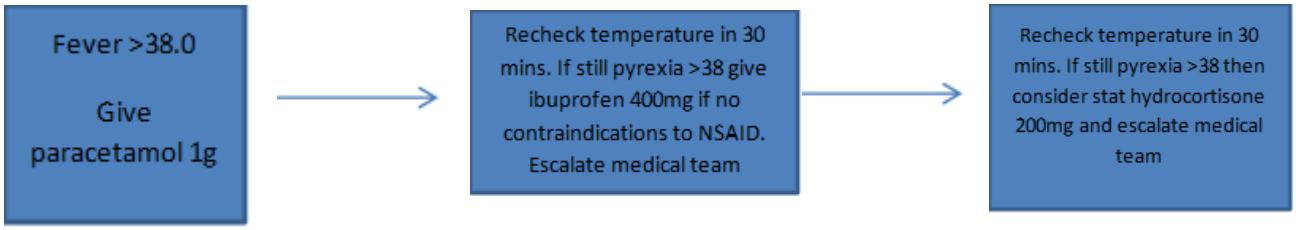
CRS Grade	Management
1	• Monitor with more frequent observations (hourly) until resolution of G1 toxicity. • Provide an antipyretic according to guidelines (see below). • Check magnesium and phosphate – if less than lower limit of normal then give IV replacement. • Resume tarlatamab at the next scheduled dose once event resolves.
2	• Manage any hypotension with IV fluid challenge (see below). • Administer of supplemental O_2 may be required if oxygen saturation drops (<94%) or patient becomes dyspnoeic (RR>20). • Repeat observations after fluid challenge and/or 0_2 supplementation. • If BP not resolving to baseline, then this should be discussed with on call Oncology SpR and Medical SpR. • CCOT should be informed. • Consider IV methylprednisolone (1mg/kg) or tocilizumab (8mg/kg and not exceeding 800mg dose).Can resume tarlatamab at the next scheduled dose once event resolves. When resuming treatment at the next planned dose, monitor patients from the start of the tarlatamab infusion for 24 hours as an inpatient
3	• As per G2 but patient will need escalation to ITU team for consideration of vasopressors and high flow oxygen. • ITU referral should involve Medical SpR and Oncology SpR. If treatment is resumed at the next planned dose, monitor patients from the start of the tarlatamab infusion for 24 hours as an inpatient • For recurrent Grade 3 reactions, permanently discontinue treatment
4	• As per G3 but for consideration of ventilator support in an ITU setting. May require additional immunosuppressives such as MMF or infliximab. • Permanently discontinue treatment.

Specific Management of Symptoms:

Rigors:

If the patient develops rigors or a temperature over 38°C:

- Monitor with more frequent observations (hourly) until resolution.
- Provide an antipyretic according to guidelines (see Below).
- If rigors consider pethidine 25mg slow IV
- Check magnesium and phosphate – if less than lower limit of normal then give IV replacement.



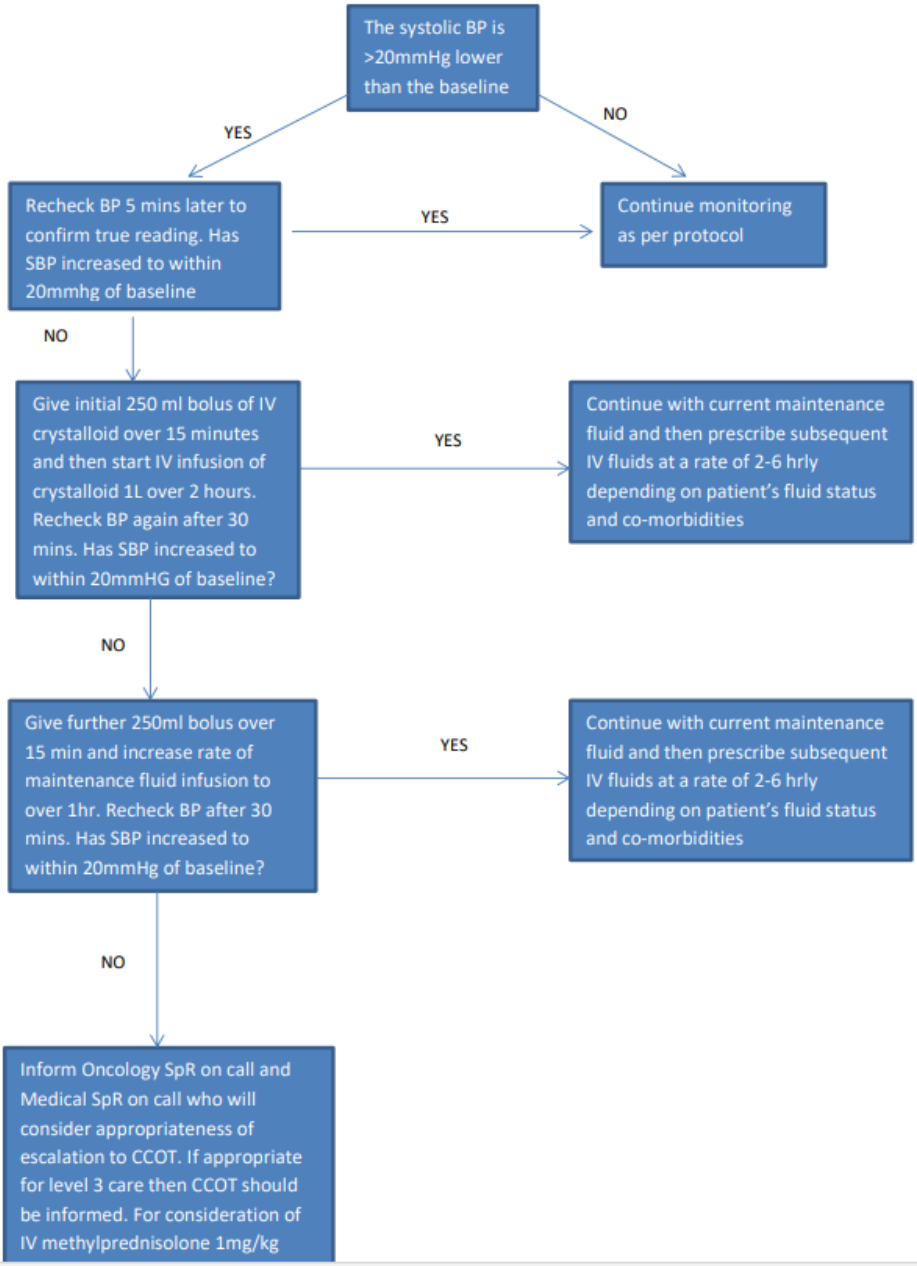
Hypoxia:

- Administration of supplemental O_2 is required if oxygen saturation drops (<94%) or patient becomes dyspnoeic (RR>20).

- Repeat observations hourly. If patient is requiring oxygen delivered by high-flow nasal cannula (> 6L/min), facemask, nonrebreather mask, or Venturi mask to maintain saturations >94% and/or has hypotension then inform oncology registrar (on call if out of hours and medical reg) and call critical care outreach.

Hypotension:

- Measure the BP 2 hourly with the patient seated. If they are ambulant around the ward or bed space, lying down in bed and/or asleep then ensure they are sat up for at least five minutes before measuring BP.
- If the systolic BP is more than 20mmHg lower than the baseline average, repeat BP 5 minutes later. If systolic BP is confirmed <20mmHg below baseline average, then inform the doctor and start IV fluids according to schedule below. If the BP recovers but then falls again, repeat the fluid challenge and iv schedule below
- If BP continues to fall below the 20mmHg from baseline threshold or patient remains/becomes symptomatic or develops hypovolemic shock, then seek advice from critical care outreach.
- Record accurate fluid balance throughout admission


The systolic BP is >20mmHg lower than the baseline
YES
NO
Recheck BP 5 mins later to confirm true reading. Has SBP increased to within 20mmhg of baseline
YES
Continue monitoring as per protocol
NO
Give initial 250 ml bolus of IV crystalloid over 15 minutes and then start IV infusion of crystalloid 1L over 2 hours. Recheck BP again after 30 mins. Has SBP increased to within 20mmHG of baseline?
YES
Continue with current maintenance fluid and then prescribe subsequent IV fluids at a rate of 2-6 hrly depending on patient's fluid status and co-morbidities
NO
Give further 250ml bolus over 15 min and increase rate of maintenance fluid infusion to over 1hr. Recheck BP after 30 mins. Has SBP increased to within 20mmHg of baseline?
YES
Continue with current maintenance fluid and then prescribe subsequent IV fluids at a rate of 2-6 hrly depending on patient's fluid status and co-morbidities
NO
Inform Oncology SpR on call and Medical SpR on call who will consider appropriateness of escalation to CCOT. If appropriate for level 3 care then CCOT should be informed. For consideration of IV methylprednisolone 1mg/kg

Rash/Itch

Initial treatment:

- Give iv Piriton 10mg initially
- If no improvement:
    - Give hydroxyzine hydrochloride (Atarax) 25mg po qds PRN

Topical treatments:

- Apply 1% hydrocortisone ointment for limited areas of itch/rash that do not respond to ant-histamine
- Use Calamine lotion and Aveeno topically can be soothing
- For all grades of skin toxicity:
    - Ensure patient is given emollients such as Epimax/E45 and are applying liberally.

Physical interventions:

- Cold showers and fans can be helpful to relieve itch
- If skin peeling (hands and feet):
    - Use creams containing 10% urea, which can be beneficial in cases of peeling skin.
- Escalation for severe reaction:
    - For reactions requiring oral steroids or montelukast, consult the Oncology SpR.
    - In the case of a Grade 3 skin reaction, contact the Medical SpR (out of hours) for a review and ensure that the Oncology SpR is informed.
    - For bullous or blistering rash, consider a referral to dermatology to rule out conditions such as bullous pemphigoid.

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

Tarlatamab 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 Tarlatamab, 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%).
Patients receiving Tarlatamab 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.

Assess ICE score and treat any ICANS as per tables below.

Table 4. Immune Effector Cell Encephalopathy (ICE) Scoring

	Task	Points
Orientation	Orientation to year, month, city, hospital	4
Naming	Ability to name 3 objects (e.g., pen, mouse, keyboard)	3
Follow commands	Ability to follow simple commands (e.g., point to the computer)	1
Language/writing	Ability to write a simple sentence	1
Attention	Ability to count backwards from 100 by 10	1

Note. Adapted from Rees et al. (2022).

ASTCT Consensus Grading for ICANS

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7–9	3–6	0–2	0 (patient is unarousable)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min), repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

ICANS grade is determined by the most severe event not attributable to any other cause.
*A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
†Attributable to no other cause (eg, no sedating medication).
‡Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE V.5.0, but they do not influence ICANS grading.
§Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE V.5.0.
ASTCT, American Society for Transplantation and Cellular Therapy; CTCAE, Common Terminology Criteria for Adverse Events; EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, Effector Cell-Associated Encephalopathy; ICP, intracranial pressure; N/A, not applicable.

Treatment of ICANS (as per Table 6 in SPC)

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

ICANS Grade[a]	Defining Symptoms	IMDELLTRA Dosage Modifications	Management
Grade 1[a]	ICE score 7-9[b] with no depressed level of consciousness.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c].	• Supportive care.
Grade 2[a]	ICE score 3-6[b] and/or mild somnolence awaking to voice.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c].	• Supportive care. • Dexamethasone[d] (or equivalent) 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.
Grade 3[a]	ICE score 0-2[b] and/or depressed level of consciousness awakening only to tactile stimulus and/or any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention and/or Focal or local edema on neuroimaging.	• Withhold IMDELLTRA until the ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c]. • If there is no improvement to grade ≤ 1 within 7 days or grade 3 toxicity reoccurs within 7 days of reinitiation, permanently discontinue IMDELLTRA. • For recurrent grade 3 events, permanently discontinue.	• Recommend intensive monitoring, e.g., ICU care. • Consider mechanical ventilation for airway protection. Dexamethasone[d] (or equivalent) 10 mg IV every 6 hours or methylprednisolone 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.
Grade 4[a]	ICE score 0[b] (patient is unarousable and unable to perform ICE) and/or Stupor or coma and/or Life-threatening prolonged seizure (> 5 minutes) or repetitive clinical or electrical 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.	• Permanently discontinue IMDELLTRA.	• ICU care. • Consider mechanical ventilation for airway protection. • High dose corticosteroids[d]. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.

[a] ICANS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019)

[b] If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (names 3 objects, e.g., point to clock, pen, button = 3 points); Following commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

Recommendations for other adverse reactions:

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

Adverse Reactions	Severity[b]	Dosage Modification[a]
Cytopenias *[see Warnings and Precautions (5.3)]*	Grade 3 or Grade 4 Neutropenia	Withhold IMDELLTRA until recovery to ≤Grade 2. Consider administration of granulocyte colony stimulating factor (G-CSF). Permanently discontinue if recovery to ≤Grade 2 does not occur within 3 weeks.
	Recurrent Grade 4 Neutropenia	Permanently discontinue IMDELLTRA
	Febrile neutropenia	Withhold IMDELLTRA until neutropenia recovers to ≤Grade 2 and fever resolves.
	Hemoglobin <8 g/dL	Withhold IMDELLTRA until hemoglobin is ≥8 g/dL.
	Grade 3 or Grade 4 Decreased platelet count	Withhold IMDELLTRA until platelet count is ≤Grade 2 and no evidence of bleeding. Permanently discontinue if recovery to ≤Grade 2 does not occur within 3 weeks.
	Recurrent Grade 4 Decreased platelet count	Permanently discontinue IMDELLTRA.

Infections *[see Warnings and Precautions (5.4)]*	All Grades	Withhold IMDELLTRA in the step-up phase in patients until infection resolves.
	Grade 3	Withhold IMDELLTRA during the treatment phase until infection improves to ≤Grade 1[a].
	Grade 4	Permanently discontinue IMDELLTRA.
Hepatotoxicity *[see Warnings and Precautions (5.5)]*	Grade 3 Increased ALT or AST or bilirubin	Withhold IMDELLTRA until adverse events improve to ≤ Grade 1.
	Grade 4 Increased ALT or AST or bilirubin	Permanently discontinue IMDELLTRA.

Adverse Reactions	Severity[b]	Dosage Modification[a]
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	Permanently discontinue IMDELLTRA.
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or 4	Withhold IMDELLTRA until recovery to ≤Grade 1 or baseline. Consider permanently discontinuing if adverse reaction does not resolve within 28 days. Consider permanent discontinuation for Grade 4 events.

Restarting Tarlatamab after dose delays.

If there is a dose delay, then restart treatment as outlined in Table 4 from SPC below with appropriate concomitant medications.

NB No dose reduction is recommended

Table 4. Recommendations for Restarting Therapy with IMDELLTRA After Dosage Delay

Last Dose Administered	Time Since the Last Dose Administered	Action[a]
1 mg on Cycle 1 Day 1	2 weeks or less (≤14 days)	Administer IMDELLTRA 10 mg, then resume with the planned 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 every 2 weeks 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.

References:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761344s000lbl.pdf

Prepared by

Prof R Board, Dr D Yiannakis and Dr A Ali

Date: November 2024
Review: November 2026