Tebentafusp Protocol

Mechanism of action

Tebentafusp is a bispecific protein therapeutic comprising a soluble, affinity-enhanced T cell receptor fused to an antibody single-chain variable fragment targeting CD3 effector domain. Tebentafusp recognizes a peptide derived from gp100, a melanocyte lineage antigen expressed strongly in tumours derived from melanocytes (i.e., melanoma), that is presented on the cell surface by HLA-A*02:01.

Eligibility for treatment

Age >18
Metastatic uveal melanoma histologically or cytologically confirmed
HLA-A 0201 positive
ECOG 0-1
Presence of untreated or symptomatic central nervous system (CNS) metastases, leptomeningeal disease, or cord compression.
Have no history of arrhythmia or significant heart disease
Have reasonable bone marrow, kidney and liver function
Patients should not be on therapeutic corticosteroids. Patients who have adrenal insufficiency and are on physiological replacement corticosteroids are eligible and will receive double their normal replacement dose on tebentafusp treatment days.

MRI of the brain will not be required prior to a patient starting tebentafusp unless clinically indicated.

Vaccinations

Inactivated (non-live) vaccine(s) should **NOT** be administered during first 4 weeks of tebentafusp therapy or administered within 24 hours before or after tebentafusp dosing.

Women of child bearing age

Women physiologically capable of becoming pregnant should be advised to use highly effective contraception methods.
In case of use of oral contraception, women should have been stable on the same oral contraceptive pill for a minimum of 3 months before beginning treatment on the program.

Dosing and Administration

Regimen	Dose	Form and route of administration	Frequency
Tebentefusp	Cycle 1 day 1: 20mcg Cycle 1 day 8: 30mcg Cycle 1 day 15: 68mcg Subsequent doses: 68mcg	100ml 0.9% sodium chloride (with 25mg albumin) given IV over 15-20 mins via a 0.2micron in-line filter	Weekly: D1,D8,D15 of each 3 week cycle

Weeks 1-3 are administered as an inpatient due to the risk of CRS and grade 3 + toxicities being highest during the first 3 cycles.

Beginning with C1D8, tebentafusp will be administered on the scheduled day (±2 days), and consecutive infusions of tebentafusp MUST be administered at least 5 days apart.

Acute reactions tend to occur 4-6 hours after drug administration. Tebentafusp should therefore be administered by 1pm wherever possible

Pre-treatment assessments:

Patients should be HLA-A 0201 positive

Baseline ECG should be performed and repeated only as clinically indicated.

Baseline echocardiogram in patients with a history of heart disease or hypertension and consider echo in all other cases based on clinical history.

A full haematology and biochemistry panel should be carried out prior to commencement of cycle 1 day 1 which should include FBC, U&E, LFT, LDH, bone profile, clotting, magnesium and phosphate within 48hours of dose.

Side effects

Common:
Cytokine release syndrome, pyrexia, chills, nausea, fatigue, hypotension, vomiting, headaches, rash, pruritis, dry skin, erythema.

Cytokine Release Syndrome: Cytokine storm is a predictable side effect of treatment with tebentafusp due to the large recruitment of T-cells. Cytokine peaks are most noticeable after the 1st dose and 3rd dose administered. This can cause significant acute blood pressure changes, febrile reaction and patients may require fluid resuscitation and other intervention including vasopressors, inotropes, supplemental O_2 and assisted ventilation in rare cases.

Symptoms and signs of CRS typically resolve after 3 days.

Monitoring Requirements

Extended Monitoring for at least 16 hours with 2 hourly vital signs is required at C1D1, C1D8, and C1D15. Patients will therefore be admitted overnight for their first 3 doses.

Monitoring at Cycle 2 Day 1 and beyond will be determined based on the toxicity observed in the individual patient in C1D1-C1D15:

- Patients experiencing a grade 2 or greater CRS event (e.g., hypotension or hypoxia) at C1D15 must continue with Extended Monitoring for the subsequent C2D1 dose. If the patient does not experience hypotension or hypoxia requiring medical intervention at the C2D1 dose administered with Extended Monitoring, then all subsequent doses can be administered with Standard Monitoring.
- If no evidence of grade 2 or greater events during C1D1-C1D15, then patients can generally undergo Standard Monitoring henceforth defined as at least 1 hour of medical observation after end of infusion at a facility with access to appropriate rescue treatments, and physician availability.

The need for Extended Monitoring outside of this scope (e.g. Cycle 2 and beyond) is determined at the discretion of the treating physician based on the patient's history and tolerance of the initial doses of tebentafusp.

Patients experiencing a prolonged break or delay in treatment, defined as interruption in treatment of more than 2 weeks AND with a history of a grade 3 or 4 event of hypotension or hypoxia with tebentafusp dosing during the first weeks of treatment, will undergo Extended Monitoring for the first dose following the prolonged break in dosing.

Day of admission for treatment:

Ensure this protocol is printed and in patient notes.

Ensure the following are aware of the patient's admission and where to access protocol online: oncology registrar and consultant on call, critical care outreach team, clinical night team and medical team on call.

Ensure the ward have sufficient stock of IV methylprednisolone in case this needs to be given out of hours.

Ensure pharmacy has tocilizumab available.

Drugs to be prescribed 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 contraindication)
Epimax/E45 cream prn

Hydrocortisone 200mg IV should be prescribed in case of infusion reaction.

A full physical examination should be carried out on day 1 cycle 1 of treatment to ensure patient is well enough to proceed with treatment, including a fluid status assessment. It may be appropriate to give pre-hydration IV fluids.

Particular attention should be paid to the patient's body temperature and blood pressure.

A raise in a patient's pre-treatment body temperature should trigger suspicion of CRS. Typically, a rise in body temperature may been seen 3-4 hours post infusion.

How to measure patient's baseline BP pre-treatment:
Seat the patient for at least 20 minutes before measuring blood pressure. Measure BP twice at an interval of at least 5 minutes apart from an upper limb (wherever possible use the same arm) with the patient remaining seated. Note the average systolic BP from these two readings (add the systolic readings and ¸ 2 = systolic average). This is the patient's baseline systolic BP. This should be recorded clearly and legibly for future reference.

Management of acute reactions

Infusion-related reactions:

Defined as any reaction occurring within 1hr of starting the infusion.

For anaphylactic reactions, proceed with standard emergency resuscitation trust guidelines.

Grade	Recommended response
1	Monitor vital signs every 15 mins until resolution of symptoms and continue infusion
2	Stop infusion but keep IV line open. Escalate to medics. Hydrocortisone 200mg IV + IV piriton 10mg to be given. IV fluids/supplemental O2 as appropriate. If reaction resolves <4hrs after starting infusion, then this can be restarted at 50% rate of infusion. Observations every 15 mins until end of infusion. Consider oral premedication with steroid and antihistamine 60 mins prior to each subsequent dose of tebentefusp.
3	Discontinue infusion immediately. • If a Grade 3 IRR improves to ≤ Grade 1 within 4 hours of onset with medical management, treatment may continue with the next scheduled dose of Tebentafusp; if resolution requires > 6 hours, treatment may continue with a ≥ 1 dose-level reduction

	• The next scheduled dose is to be delivered using a rate of infusion not to exceed 50% of rate used when the IRR occurred • Oral premedications are to be given within 60 minutes prior to the next scheduled dose of Tebentafusp If Grade 3 IRR recurs after restarting Tebentafusp treatment, dosing should be permanently discontinued unless the Consultant believes the overall benefit-risk favors continued treatment
4	As per G3. Permanently discontinue tebentefusp.

CRS is the most common associated toxicity. Grading of severity is based on the American Society for Transplantation and Cellular Therapy (ASTCT).

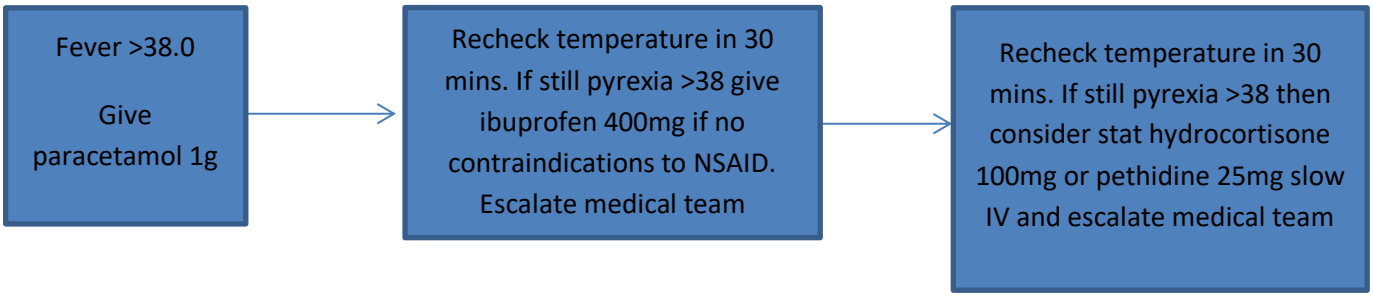
Grade	**Fever**	**with Hypotension**	**and/or Hypoxia**
1	≥ 38.0 °C	None	None
2	≥ 38.0 °C	Not requiring vasopressors	Requiring oxygen delivered by low-flow nasal cannula (≤ 6 L/min)
3	≥ 38.0 °C	Requiring a vasopressor with or without vasopressin	Requiring oxygen delivered by high-flow nasal cannula (> 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)

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. Can continue with tebentefusp
2	Manage any hypotension with IV fluid challenge (see below). Administration of supplemental O2 may be required if oxygen saturation drops (<94%) or patient becomes dyspnoeic (RR>20). Repeat observations after fluid challenge and/or 02 supplementation. If BP not resolving to baseline, then this should be discussed with on call Oncology SpR and Medical SpR. CCOT should be informed. There should be

	consideration of IV methylprednisolone (1mg/kg) or tocilizumab (8mg/kg and not exceeding 800mg dose).
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.
4	As per G3 but for consideration of ventilator support in an ITU setting. May require additional immunosuppressives such as MMF or infliximab.

Rigors:
Fever has been identified as a hallmark sign of CRS.
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). Check magnesium and phosphate – if less than lower limit of normal then give IV replacement. Can continue with tebentefusp



Hypoxia:

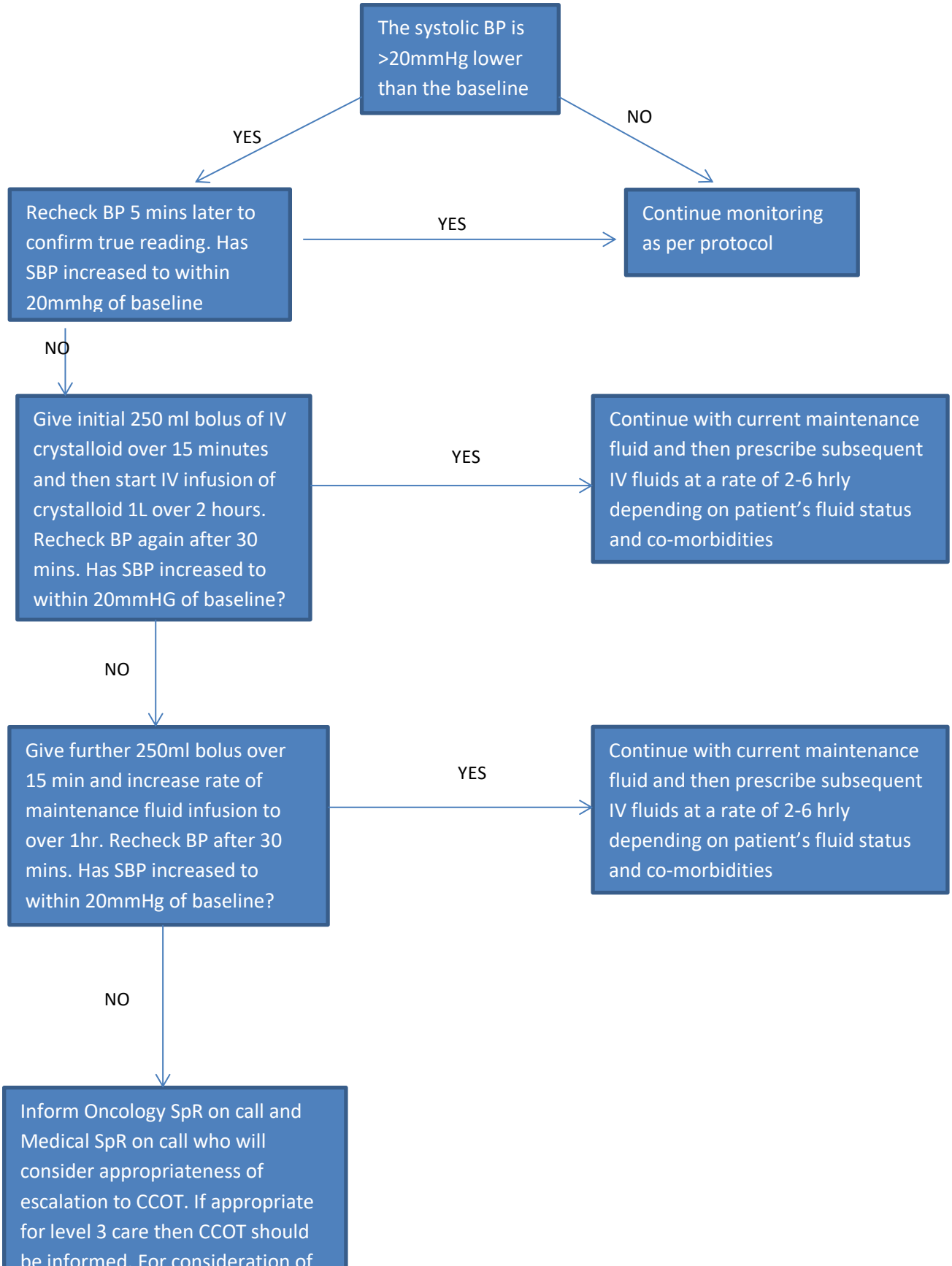
Administration of supplemental O2 is required if oxygen saturation drops (<94%) or patient becomes dyspnoeic (RR>20). Repeat observations hourly. If patient is requiring oxygen delivered by high-flow nasal cannula (> 6L/min), facemask, nonrebreather mask, or Venturi mask to maintain saturations >94% 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.

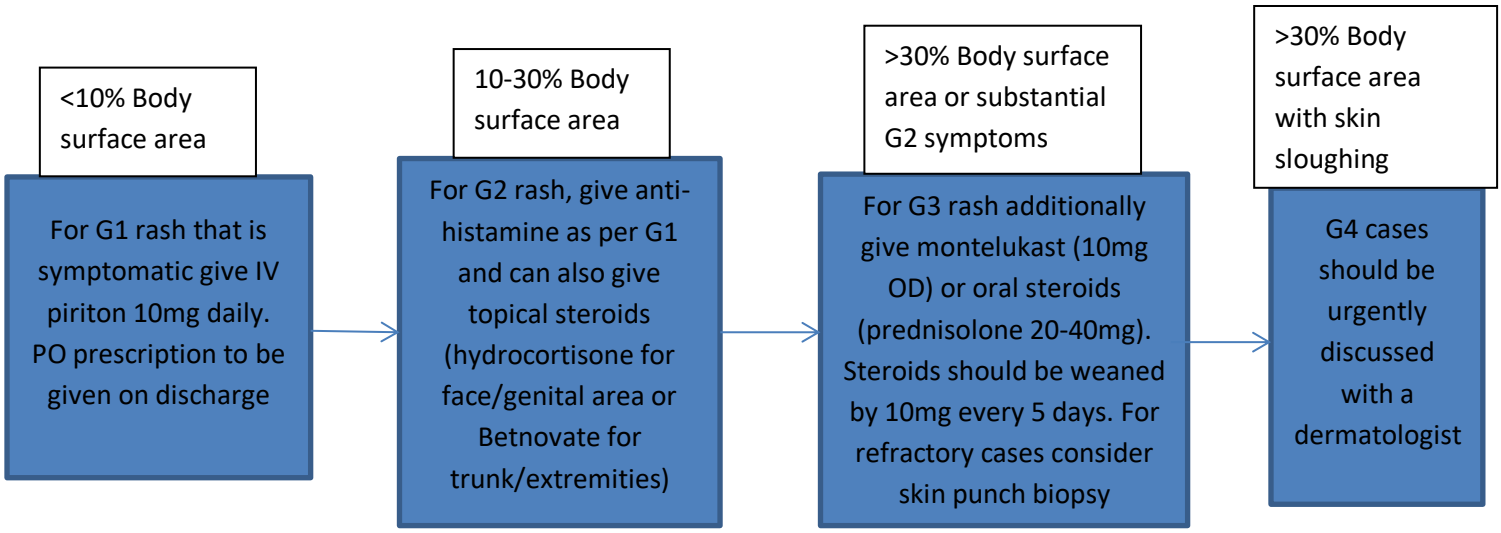
If BP continues to fall below the 20mmHg from baseline threshold or patient remains/becomes symptomatic or develops hypovolemic shock then seek advice from critical care outreach.

Record accurate fluid balance throughout admission



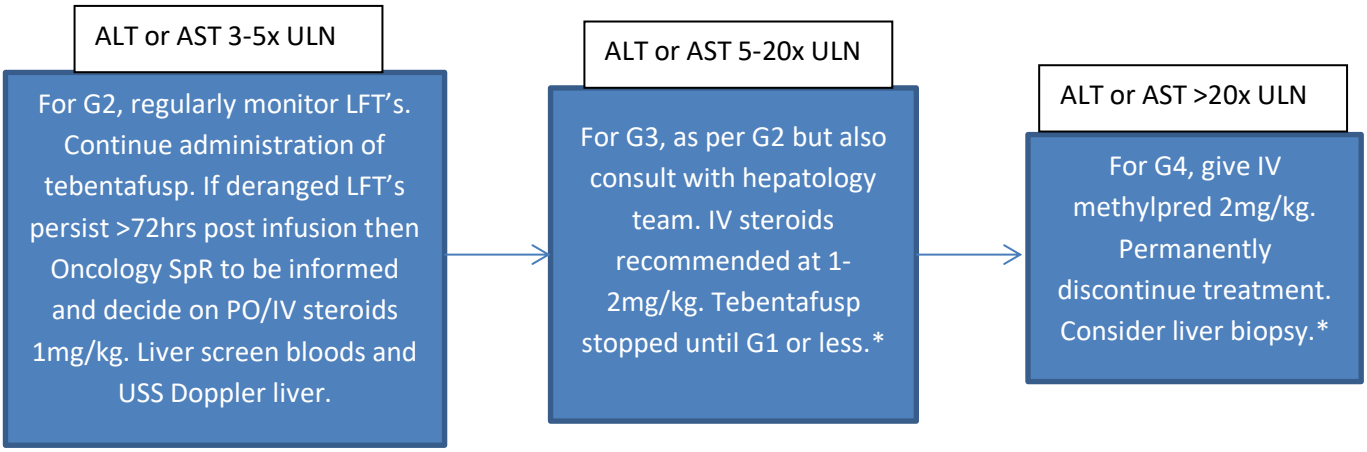
Rash:

For rash/pruritis	
Grade	Dose Recommendations
1	May continue dosing.
2	May continue dosing.
3	Do not administer study medications until rash / pruritus has improved to Grade ≤ 1. • If Grade 3 rash / pruritus resolves to ≤ Grade 1 in < 7 days, treatment may continue at the same dose level • If Grade 3 rash / pruritus resolves to ≤ Grade 1 in 7 to 21 days, restart with ≥1 dose-level reduction in Tebentafusp • If Grade 3 rash / pruritus does not resolve within 21 days, permanently discontinue all study medications.
4	Discontinue all study medications.



Ensure patient is given emollients such as Epimax/E45 for all grade of skin toxicity and are applying liberally.
Cold showers and fans can be helpful as physical interventions for the itch.
If there is peeling of the skin on hands and feet – then creams containing 10% urea can be beneficial
In the event of reactions that may require oral steroids or montelukast, please consult oncology SpR.
For Grade 3 skin reaction please contact Medical SpR out of hours for a review in addition to informing oncology SpR.
If it is a bullous/blistering looking rash, consider referral to dermatology to rule out other conditions e.g. bullous pemphigoid.

Hepatic Toxicity:



*For isolated ALT and/or AST elevation (>5-8 × ULN) or isolated total bilirubin elevation (>3-5 × ULN) that resolves to Grade ≤1, dosing at the current dose level may resume.
For isolated ALT and/or AST elevation (>8 × ULN) or isolated total bilirubin elevation (>5 × ULN) that resolves to Grade ≤1, dosing should be permanently discontinued unless consultant believes the overall benefit-risk favours continued treatment, in which case dosing may resume. Study medication(s) must be permanently discontinued for ALT and/or AST elevation (>3 × ULN) with concurrent elevation in total bilirubin (>2 × ULN) and/or INR (>1.5 × ULN, patients not receiving anticoagulants).

Dose Reduction/Adjustments following an adverse reaction

For grade ≥2 CRS, withhold next scheduled dose of tebentafusp until CRS has resolved. In the case of grade ≥3 CRS, dose reduction will be required.

For CRS	
Grade	Dosing Recommendations
1	**May continue dosing.**
2	Do not administer next scheduled dose of Tebentafusp until CRS has resolved. • Extended Monitoring until discharge is required for the next scheduled dose of Tebentafusp

3	Do not administer next scheduled dose of Tebentafusp until CRS has resolved. Treatment may continue provided all the following conditions are met: • Extended Monitoring with assessment of vital signs approximately every 2-4 hours post-EOI until discharge is required after the next two scheduled doses of Tebentafusp • Reduce the dose of Tebentafusp by ≥ 1 dose level • Consider premedication within 60 minutes prior to the start of the next scheduled infusion • If the patient experiences ≤ Grade 1 CRS following the first reduced dose, then the next dose of Tebentafusp should be administered at the reduced dose without premedication, but must include Extended Monitoring including assessment of vital signs approximately every 2-4 hours post-EOI until discharge • If the patient no longer requires premedication and tolerates at least four subsequent doses of Tebentafusp without Grade 2 or higher CRS, then (with consultation of consultant) dose escalation to the original dose may be considered (with Extended Monitoring and assessment of vital signs approximately every 2-4 hours post-EOI until discharge following the next higher dose) Any patient that experiences recurrence of Grade 3 CRS following retreatment should permanently discontinue study treatment unless the Consultant believes the overall benefit-risk favors continued treatment
4	Study medication(s) must be permanently discontinued.

Dose reduction instructions:

Dose reductions of Tebentafusp for toxicity is as follows: from a starting dose Tebentafusp dose of 68 mcg, the dose will be reduced to 54 mcg for any toxicity requiring dose reduction. The dose may be reduced further to 50 mcg for recurrent toxicity. Patients who require more than 2 dose reductions of Tebentafusp should discontinue treatment. All dose modifications should be based on the worst preceding toxicity. Once a dose has been reduced it may be increased to the initial dose level if there is no recurrence of toxicity with subsequent doses of Tebentafusp.

January 2025
Review January 2027