

Tebentafusp

Indication

HLA-A*02:01-positive unresectable or metastatic uveal melanoma in adults.

Regimen details

Tebentafusp

Cycle 1 day 1: 20mcg

Cycle 1 day 8: 30mcg

Cycle 1 day 15: 68mcg

Subsequent doses: 68mcg

Weeks 1-3 are administered as an inpatient due to the risk of cytokine release syndrome (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

Cycle frequency

D1,D8,D15 of each 3 week cycle.

Number of cycles

Continue treatment until disease progression or unacceptable toxicity. Atypical responses similar to immune checkpoint inhibitors have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Administration

100ml 0.9% sodium chloride (with 25mg albumin) given IV over 15-20 mins via a 0.2micron in-line filter

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.

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.

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 be 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 $\div 2$ = systolic average). This is the patient's baseline systolic BP. This should be recorded clearly and legibly for future reference.

Subsequent treatment doses from cycle 2:

After 68 mcg dose level is tolerated (i.e., absence of Grade ≥ 2 hypotension requiring medical intervention), subsequent doses can be administered in appropriate out-patient ambulatory care setting. Observe patients for a minimum of 30 minutes following each infusion.

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.

Pre-medication

None

Emetogenicity

Low emetic potential.

Additional supportive medication

Tocilizumab vials should be sent to the ward prior to cycle 1 in case it is required for cytokine release syndrome.

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.

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

Extravasation

Tebentafusp is neutral (group 1)

Investigations – pre first cycle

- Baseline ECG should be performed before and after tebentafusp administration during the first 3 weeks.
 - Withhold tebentafusp if **QTcF >500 ms or increases by ≥60 ms from baseline**, with assessment/correction of reversible causes before restarting
- Baseline echocardiogram should be performed in all patients before starting tebentafusp.

For cycle 1 including days 8 and 15 – wait for bloods before administering.

Investigation	Validity period
FBC	48 hours
U+E (including creatinine)	48 hours
LFT (including AST)	48 hours
LDH	48 hours
Bone profile	48 hours
Clotting	48 hours
Serum magnesium	48 hours
Serum phosphate	48 hours
ECG	Before and after the first 3 doses as above
Echocardiogram	Before initiation

Investigations –pre subsequent cycles

Investigations – pre cycle 2

Investigation	Validity period
FBC	48 hours
U+E (including creatinine)	48 hours
LFT (including AST)	48 hours

Investigations – pre cycle 3

Investigation	Validity period*
FBC	Within 72 hours of day 1 only
U+E (including creatinine)	Within 72 hours of day 1 only
LFT (including AST)	Within 72 hours of day 1 only

*for patients stable on treatment for > 6 months consider reducing frequency of pre-assessments and blood tests to 6 weekly.

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	$\geq 1.0 \times 10^9/\text{L}$
Platelet count	$\geq 75 \times 10^9/\text{L}$
Creatinine clearance	$\geq 30 \text{ mL/min}$
Bilirubin	$\leq 1.5 \times \text{ULN}$
ALT/AST	$< 5 \times \text{ULN}$

Dose modifications:

Haematological toxicity

Tebentafusp is not expected to cause haematological toxicity. If neutrophils $< 1.0 \times 10^9/L$ or platelets $< 75 \times 10^9/L$, discuss with consultant.

Renal impairment

No dose adjustment is required for mild or moderate renal impairment ($CrCl \geq 30$ ml/min). There is no data available for dosing in severe renal impairment so patients should be treated with caution.

Hepatic impairment

No dose adjustment is required for mild hepatic impairment (bilirubin $\leq 1.5 \times$ ULN). There is no information available for treatment of patients with moderate or severe hepatic impairment. See below for management of elevated LFTs during treatment.

Dose Reduction/Adjustments following an adverse reaction

For cytokine release syndrome: For grade ≥ 2 CRS, withhold next scheduled dose of tebentafusp until CRS has resolved

CRS Grade*	Management
Grade 1 Temperature $\geq 38^\circ C$ No hypotension or hypoxia	Treat for symptoms as appropriate. Monitor for escalation in CRS severity
Grade 2 Temperature $\geq 38^\circ C$ Hypotension that responds to fluids and does not require vasopressors. Oxygen requirement includes low flow nasal cannula (delivery of oxygen ≤ 6 L/min) or blow-by	Symptom management as per Grade 1 in addition to the following measures: Administer bolus intravenous fluids as needed for hypotension Manage oxygen requirement with supplemental oxygen and additional respiratory support as needed. Increase monitoring to determine resolution or escalation in severity If Grade 2 CRS symptoms do not rapidly improve to Grade ≤ 1 within 2-3 hours, then treat as Grade 3 For Grade 2 CRS that is persistent (lasting 2-3 hours) or recurrent (occurrence of $\geq$ Grade 2 CRS with more than one dose), administer corticosteroid premedication (e.g. dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose
Grade 3 Temperature $\geq 38^\circ C$ Require a vasopressor with or without vasopressin. Require high flow nasal cannula (delivery of oxygen > 6 L/min), face mask or non-rebreather mask or Venturi mask	Management per Grade 2 and include the following measures: Administer high-dose intravenous corticosteroid (e.g. 2 mg/kg/day methylprednisolone or equivalent) Increase monitoring to determine resolution or escalation in severity Consider administering tocilizumab. Withhold tebentafusp until Grade ≤ 1 . At next treatment, resume tebentafusp at same dose level (i.e. do not escalate) after appropriate risk versus benefit assessment and monitor patient accordingly. Once dose level is tolerated, can resume pre-planned dosing schedule For Grade 3 CRS, administer corticosteroid premedication (e.g. dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose
Grade 4 Temperature $\geq 38^\circ C$ Require multiple vasopressors. Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation).	Permanently discontinue tebentafusp Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)

For acute skin reactions and elevated liver enzymes:

Adverse Reactions	Severity^a of Adverse Reaction	Management
Acute skin reactions (see section 4.4)	Grade 2 or 3	Use local skin management and systemic antihistamine regimen. Topical corticosteroid treatment can be considered for symptomatic rash that does not respond to anti-pruritic regimen. Consider systemic steroids for persistent or severe symptoms. Withhold tebentafusp until Grade ≤ 1 Resume tebentafusp at same dose level (i.e., do not escalate if Grade 3 skin reactions occurred during initial dose escalation; resume escalation once dosage is tolerated)
	Grade 4	Permanently discontinue tebentafusp Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)
Elevated liver enzymes (see section 4.4)	Grade 3 or 4 ^a	Withhold tebentafusp until $\leq$ Grade 1 or baseline. Resume tebentafusp at same dose level if the elevated liver enzymes occur in the setting of Grade 3 CRS; resume escalation if next administration is tolerated. If the elevated liver enzymes occur outside the setting of Grade 3 CRS resume escalation if the current dose is less than 68 mcg, or resume at same dose level if dose escalation has completed Administer intravenous corticosteroids if no improvement within 24 hours
Other clinically relevant adverse reactions	Grade 3 ^a	Withhold tebentafusp until $\leq$ Grade 1 or baseline Resume tebentafusp at same dose level (i.e., do not escalate if other Grade 3 adverse reaction occurred during initial dose escalation; resume escalation once dosage is tolerated)
	Grade 4 ^a	Permanently discontinue tebentafusp

Adverse effects - for full details consult product literature/ reference texts

- Serious side effects**

Infusion related reactions – See information below

Cytokine Release Syndrome: Cytokine storm is a predictable side effect of treatment with tebentafusp due to the large recruitment of T-cells. CRS occurs predominantly during the first three tebentafusp doses and generally decreases in frequency and severity with subsequent doses. This can cause significant acute blood pressure changes, febrile reaction and patients may require fluid resuscitation and other intervention including vasopressors, inotropes, supplemental O₂ and assisted ventilation in rare cases.

Symptoms and signs of CRS typically resolve with treatment after 3 days.

- Frequently occurring side effects**

Pyrexia, chills, nausea, fatigue, hypotension, vomiting, headaches, rash, pruritis, dry skin, erythema.

- Other side effects**

Significant drug interactions – for full details consult product literature/ reference texts

No formal drug interaction studies have been performed with tebentafusp.

Initiation of tebentafusp treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug-drug interaction risk is during the first 24 hours of the first three doses of tebentafusp in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (e.g., warfarin) or drug concentrations (e.g., cyclosporine). Adjust the dose of the concomitant drug as needed.

Additional comments

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 $\leq$ 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.

Cytokine release syndrome:

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	$\geq 38.0^{\circ}\text{C}$	None	None
2	$\geq 38.0^{\circ}\text{C}$	Not requiring vasopressors	Requiring oxygen delivered by low-flow nasal cannula ($\leq 6\text{ L/min}$)
3	$\geq 38.0^{\circ}\text{C}$	Requiring a vasopressor with or without vasopressin	Requiring oxygen delivered by high-flow nasal cannula ($> 6\text{L/min}$), facemask, nonrebreather mask, or Venturi mask

4	$\geq 38.0^{\circ}\text{C}$	Requiring multiple vasopressors (excluding vasopressin)	Requiring oxygen delivered by positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)
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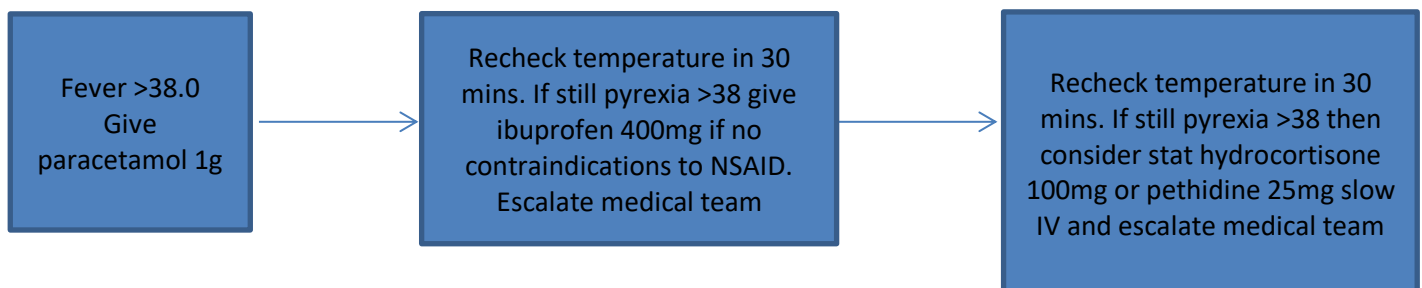
CRS Grade	Management
1	Monitor with more frequent observations (hourly) until resolution of G1 toxicity. Provide an antipyretic according to guidelines (see Below). Check magnesium and phosphate – if less than lower limit of normal then give IV replacement. Can continue with tebentefusp
2	Manage any 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 O2 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:

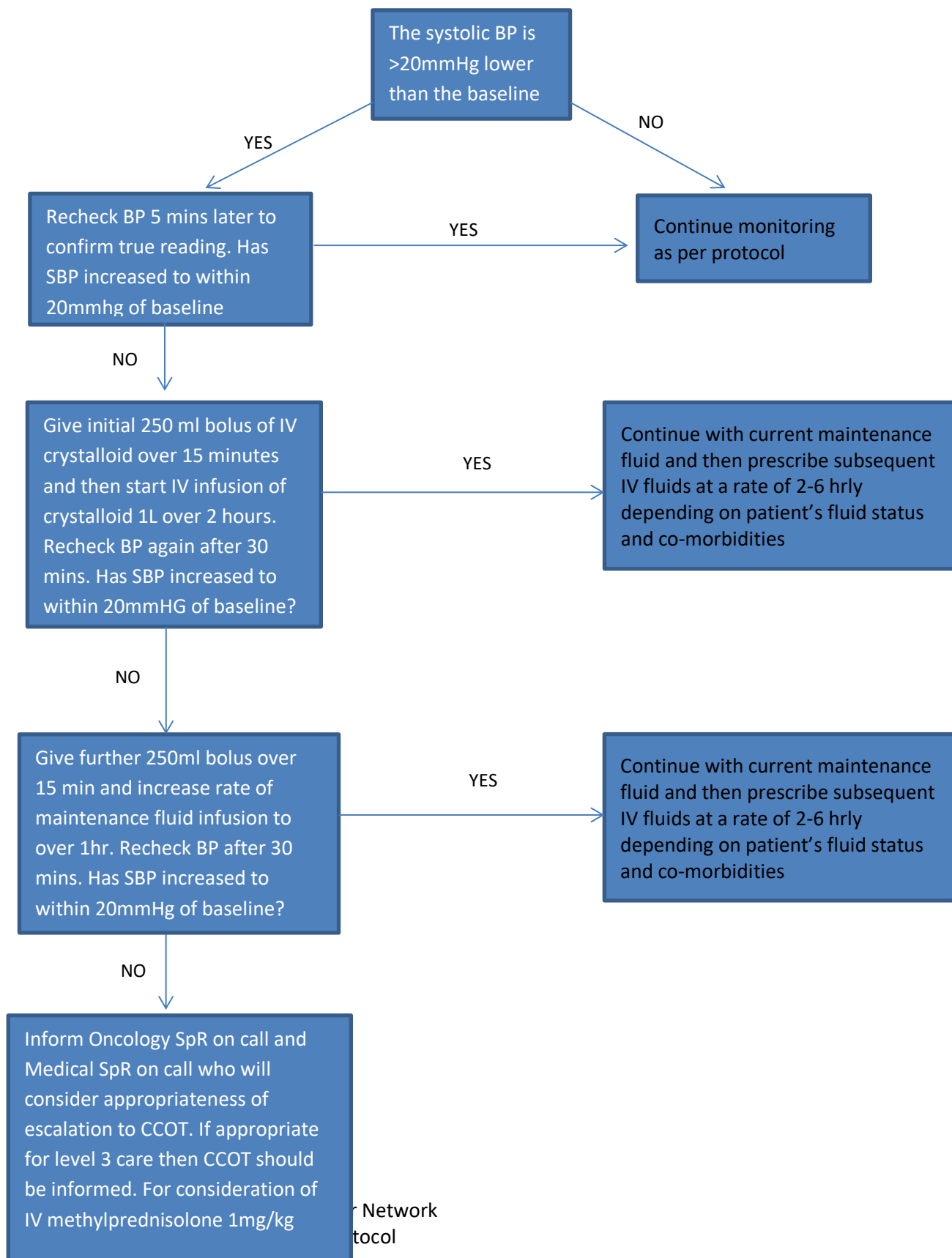
Administration of supplemental O2 is required if oxygen saturation drops (<94%) or patient becomes dyspnoeic (RR>20). Repeat observations hourly. If patient is requiring oxygen delivered by high-flow nasal cannula (> 6L/min), facemask, nonrebreather mask, or Venturi mask to maintain saturations >94%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

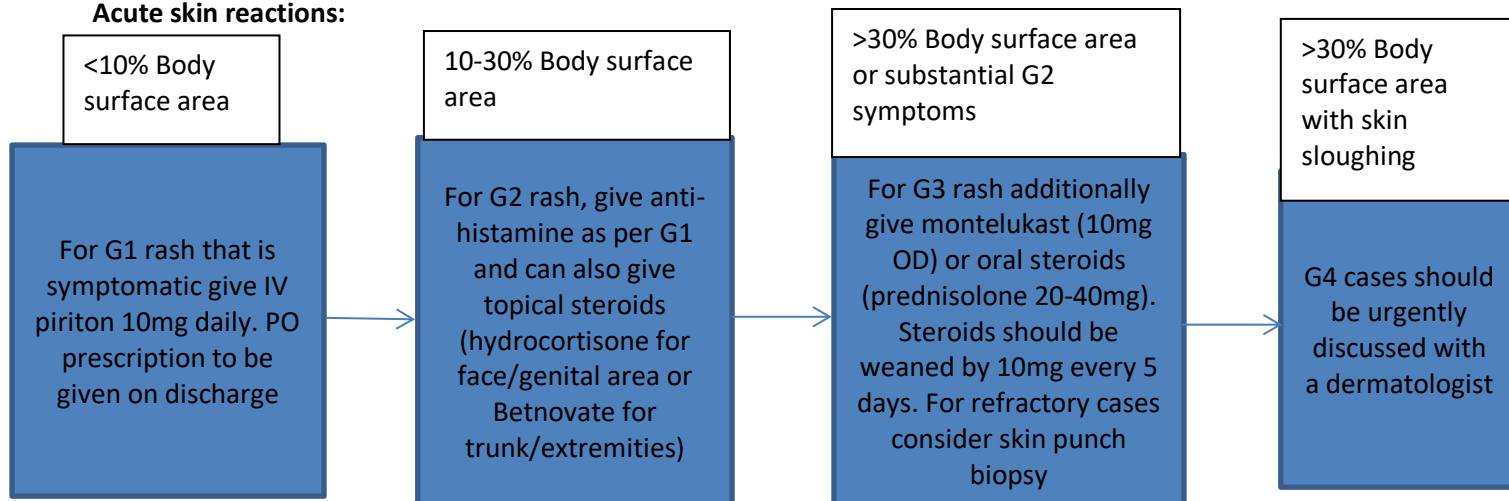
If BP continues to fall below the 20mmHg from baseline threshold or patient remains/becomes symptomatic or develops hypovolemic shock then seek advice from critical care outreach.

Record accurate fluid balance throughout admission



Rash:

Acute skin reactions:



Ensure patient is given emollients such as Epimax/E45 for all grade of skin toxicity and are applying liberally.

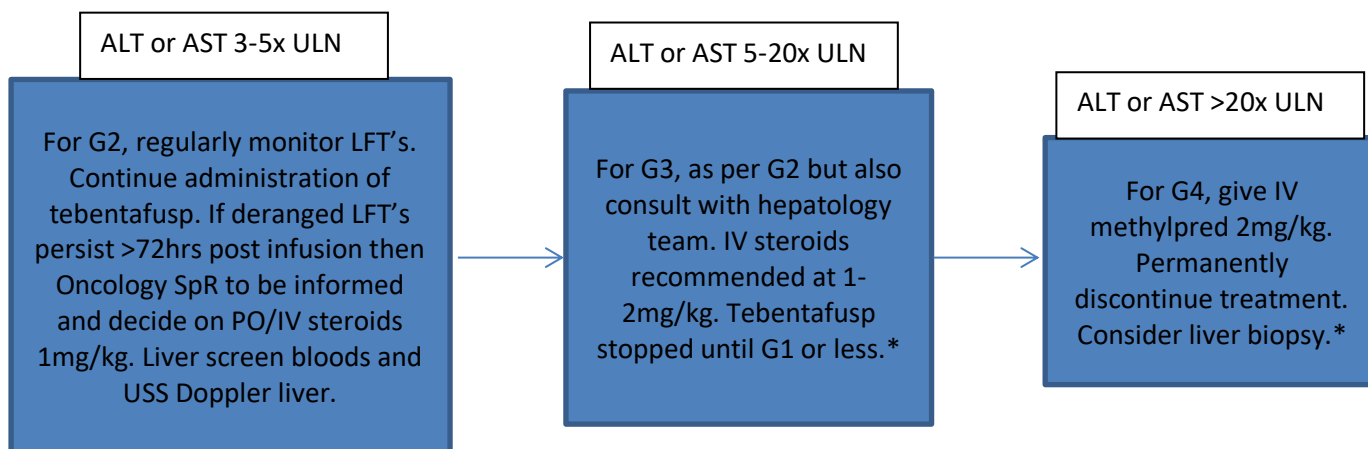
Cold showers and fans can be helpful as physical interventions for the itch.

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 ($>5-8 \times \text{ULN}$) or isolated total bilirubin elevation ($>3-5 \times \text{ULN}$) that resolves to Grade ≤ 1 , dosing at the current dose level may resume.

For isolated ALT and/or AST elevation ($>8 \times \text{ULN}$) or isolated total bilirubin elevation ($>5 \times \text{ULN}$) 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. Tebentafusp must be permanently discontinued for ALT and/or AST elevation ($>3 \times \text{ULN}$) with concurrent elevation in total bilirubin ($>2 \times \text{ULN}$) and/or INR ($>1.5 \times \text{ULN}$, patients not receiving anticoagulants).

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.

References

- Summary of Product Characteristics Nivolumab via www.medicines.org.uk

THIS PROTOCOL HAS BEEN DIRECTED BY THE DESIGNATED LEAD CLINICIAN FOR MELANOMA

Whilst every effort is made to ensure the accuracy of the information in a given protocol it cannot be guaranteed that the protocol is fully up to date. Cancer treatment can be dynamic in nature. Decisions on SACT must therefore be based on the independent judgement of the clinician with reference to changing information on the medicine (eg, available literature and SmPC) and evolving medical practices.

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VERSION: 2
