Treatment Guideline: Tebentafusp for the Treatment of Metastatic Uveal Melanoma in HLA-A*02:01 Positive Patients

Introduction:

Tebentafusp is a novel immunotherapy that has been shown to improve survival in patients with metastatic uveal melanoma. It is given weekly by IV infusion. Patients require admission for their first three treatments for overnight monitoring and management of cytokine release syndrome (CRS). Thereafter, tebentafusp can usually be administered safely as an outpatient. Fortunately, the rates of severe CRS (≥grade 3) are very low (≤1%). This guideline outlines the identification and management of adverse events that may be experienced during treatment, as well as procedure on admission to the ward.

Treatment setting:

Patients should be admitted to Lilleybrook or Rendcomb ward for the first three infusions for a minimum of 16 hours of monitoring.

Admission should be planned for early/mid-week. Patients will be assessed in chemo clinic on a Tuesday with blood results to authorize treatment. The prescriber will liaise with the oncology bed manager to confirm if treatment is proceeding. Once admission is confirmed, the prescriber should inform Acute Care Response Team (ACRT) / Department of Critical Care (DCC) team due to the low risk of severe CRS that may warrant critical care input.

Patients should be admitted the night before treatment, allowing time for pharmacy to prepare the drug for administration the following morning. Tebentafusp administration must be completed within normal working hours and ideally by early afternoon.

If patients tolerate the first three infusions, further treatment can be given as an outpatient. Definitions of when to transition to outpatient treatment are outlined in the Managed Access Program protocol.

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On admission to the ward:

Ward doctors:	Prescribe the following PRN medications on the inpatient drug chart: Chlorphenamine 10mg IV QDS PRN Paracetamol 1g PO/IV QDS PRN Hydroxyzine hydrochloride (Atarax) 25mg PO QDS PRN Ibuprofen 400mg PO TDS PRN (if no contraindication) Aveeno cream PRN Hydrocortisone 100mg IV PRN (under consultant direction only)
Nursing staff:	Seat patient for a minimum of 20 minutes prior to measuring blood pressure (BP). Measure BP twice at an interval of 5 minutes apart from an upper limb (use the same arm where possible) with the patient remaining seated. Document the baseline average systolic BP from these two readings (add the 2 systolic readings and divide by 2). Record fluid balance accurately for duration of admission.

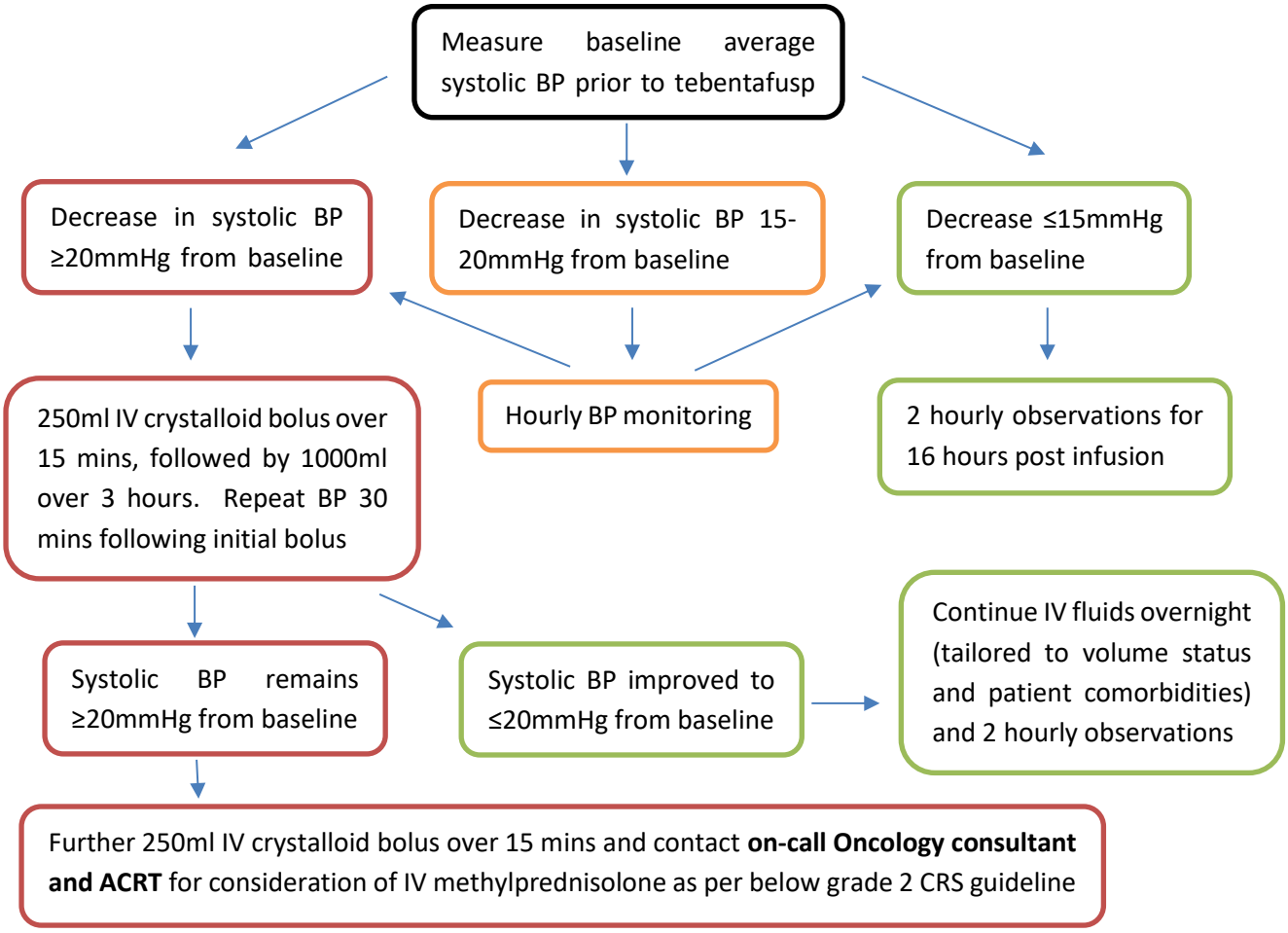
Administration of tebentafusp:

Tebentafusp should be administered as an IV infusion through a peripheral or central line via a low protein binding 0.2 micron in line filter giving set. Post-infusion, the line should be flushed with 0.9% Sodium Chloride.

Following administration of tebentafusp:

Monitor observations 2 hourly (BP should be taken with the patient seated).
If the systolic BP is ≥20mmHg lower than the baseline average, repeat BP measurement 5 minutes later. If systolic BP is confirmed ≥20mmHg lower than the baseline average, inform the ward doctor to start IV fluids according to below schedule.

Fluid management schedule:



Assessment and management of rash/pruritus:

Grade 1: <10% BSA with or without symptoms

Grade 2: 10-30% BSA or intermittent pruritus

Grade 3: >30% BSA or grade 2 with substantial symptoms or constant pruritus

Grade 4: skin sloughing >30% BSA with associated symptoms

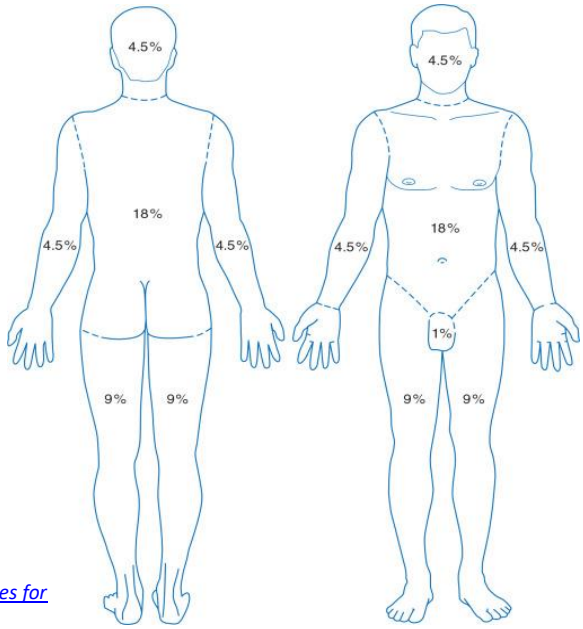


Figure 1: Body surface area (BSA). Reference: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines. Accessed 12/08/22 via [Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (annalsofoncology.org)]

Treatment of grade 2/3 symptoms:
Give IV chlorphenamine 10mg. If no improvement, give Hydroxyzine 25mg PO TDS PRN.
Apply hydrocortisone 1% ointment to limited areas that do not respond to antihistamines.
Apply topical Aveeno.
Consider hydrocortisone if persistent or severe symptoms 100mg IV (must be discussed with consultant).

Treatment of grade 4 symptoms:
As above. Administer 2mg/kg/day IV methylprednisolone.
Permanently discontinue tebentafusp.

Management of rigors:

If the patient develops rigors or a temperature over 38 °C, give paracetamol 1g PO/IV initially.
If this is not effective, give ibuprofen 400mg PO (if no contraindication).
If the patient remains febrile, consider 100mg IV hydrocortisone bolus (must be discussed with consultant).

ASTCT CRS grading criteria:

Grade	Fever	With Hypotension	And/or hypoxia
1	≥ 38.0 °C	None	None
2	≥ 38.0 °C	Responds to fluids and does not require vasopressors	Requiring oxygen via nasal cannula (≤6L/min) to maintain target saturations
3	≥ 38.0 °C	Not responding to fluids, requiring a vasopressor with or without vasopressin	Requiring oxygen delivered by high-flow nasal cannula (>6L/min), via facemask, non-rebreather mask or Venturi mask
4	≥ 38.0 °C	Requiring multiple vasopressors (excluding vasopressin)	Requiring oxygen delivered by positive pressure (CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT: American Society for Transplantation and Cellular Therapy

Management of CRS according to grade:

Grade	
1	Treat symptoms as per management of fever/rigors section.
2	**Involve ACRT (bleep 1700) and contact on-call Oncology consultant (bleep 1167 or via switchboard).** Treat symptoms as per management of fever/rigors section. Bolus IV fluids for hypotension as per fluid management schedule. Manage oxygen requirement with supplemental oxygen and additional respiratory support as needed. Increase observations to 1 hourly. If grade 2 symptoms do not rapidly improve to grade ≤1 within 2 hours, treat as grade 3.
3/4	As per grade 2. **Involve ACRT and contact on-call Oncology consultant.** Administer systemic immunosuppressive agent (methylprednisolone 2mg/kg daily). Consider escalation to second line immunosuppressive agents (tocilizumab, mycophenolate or infliximab). Treat persistent hypotension with vasopressors as indicated. Escalate level of care to HDU/ITU as indicated.

Further information:

If you have any questions or comments on this guideline, please contact Dr Ella Daniels (Specialist Registrar in Medical Oncology) or Dr David Farrugia (Consultant Medical Oncologist and lead for tebentafusp).

Treating melanoma consultants: Dr David Farrugia and Dr Marios Decatris.

References:

Nathan P et al. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med. 2021 Sep 23;385(13):1196-1206.

Immunocore Tebentafusp – Managed Access Protocol v1.1 April 2021

Lee DW et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638.

Summary of Product Characteristics Tebentafusp (Immunocore Limited) accessed 8 August 2022 via www.medicines.org.uk

Mount Vernon Cancer Centre 'Ward Management of Patients receiving Tebentafusp' guidelines

Bristol Haematology and Oncology Centre 'Treatment of Uveal Melanoma Patients with Tebentafusp' standard operating procedure