SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Tebentafusp (Managed Access Program) For the treatment of metastatic uveal melanoma

PROTOCOL REF: MPHATMUM
(Version No. 1.0)

Approved for use in:

- Uveal Melanoma - first or subsequent line of therapy in the palliative setting for patients with:
  - Metastatic or unresectable uveal melanoma
  - HLA-A*02:01 positive
  - Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Tebentafusp is available through a Managed Access Program (MAP) and provided free of charge via Clinigen Healthcare Ltd.
- Patient must be registered with the Named Patient Program from the Clinigen Group
- Stock must be ordered via the ClinigenDirect Online Ordering Portal. Please give Pharmacy advance notice of new patients.

Please NOTE: this is unlicensed use.
Please refer to the 'CCC Unlicensed Medicines Policy' for full details on consenting, prescribing, documentation and supply of unlicensed medicines. As per trust policy please provide the 'Unlicensed Medicines Information' to patients and carers as appropriate

Dosage:

Drug	Dose	Route	Frequency
Tebentafusp	**20 micrograms**	IV infusion	Cycle ONE day ONE
	30 micrograms		Cycle ONE day EIGHT
	68 micrograms		Cycle ONE day FIFTEEN then continuing ONCE weekly until disease progression or intolerable toxicity

To be given as an inpatient for the first three doses (cycle one day one, eight and fifteen) and then outpatient thereafter (cycle two and beyond).

Patients who experience a grade 2 or greater cytokine release syndrome event (e.g. hypotension or hypoxia) at C1D15 must continue with extended monitoring for the subsequent C2D1 dose. If the patient doesn't 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.

Administration:

Administer the infusion over 15 minutes through a dedicated intravenous line. A sterile, non-pyrogenic, low protein binding 0.2 micron in-line filter infusion set should be used. Human albumin solution (HAS) is used in the aseptic preparation of tebentafusp and is present in the final product.

On admission to the ward:

- Seat the patient for at least 20 minutes before measuring blood pressure
- Measure BP twice from an upper limb at an interval of at least five minutes apart (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 divide by two to obtain the systolic average)
- This is the patient's baseline systolic BP
- Record fluid balance during the duration of admission

Following inpatient administration of tebentafusp:

Patients must have extended monitoring for at least 16 hours, and vital signs (blood pressure, heart rate, temperature and pulse oximetry) taken every 2-4 hours:

- Measure the BP two 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 15-20mmHg lower than the baseline average then commence hourly BP monitoring. If systolic BP drops below 20mmHg of baseline then inform the ward doctor who will start IV fluids according to the schedule below
- If the systolic BP is more than 20mmHg lower than the baseline average, repeat BP five minutes later. If systolic BP is confirmed <20mmHg below baseline average then inform the ward doctor who will start IV fluids according to schedule below

Fluid management:

- Give 250 ml bolus of IV crystalloid over 15 minutes and then start IV infusion of crystalloid 1L over two hours
- Check BP 30 minutes after IV bolus. If BP has responded and has elevated above 20mm threshold, continue IV infusion overnight with maintenance fluids (e.g. crystalloid 1L over four hours) and check BP every two hours. Further 250ml bolus over 15 minutes should be given if BP falls again below 20mmHg from baseline average and maintenance fluid rate increased by 50%
- If BP continues to fall below the 20mmHg from baseline threshold or patient remains unwell despite appropriate fluid infusion, treat with hydrocortisone 100mg IV, escalate to the medical team

Cytokine Release Syndrome:

During trials 89% of patients experienced some grade of cytokine release syndrome (CRS) although this was almost always low grade (<5% grade 3 or 4). If experienced this should be escalated to the medical team as a priority and managed per local guidance:

https://www.clatterbridgecc.nhs.uk/application/files/7715/8565/0569/Immune-Related_Adverse_Event_Guideline_-_Cytokine_Release_Syndrome_V1.0.pdf

Emetogenic risk:

Low

Supportive treatments:

Chlorphenamine 10mg/ml injection – 10mg as required every four to six hours up to four times per day
Hydroxyzine 25mg tablets – 25mg as required every eight hours up to three times per day
Paracetamol 500mg tablets – 1g as required every four to six hours up to four times per day
Aquamax cream – apply topically as required
Cetraben cream – apply topically as required

Extravasation risk:

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal	Omit if creatinine clearance (calculated using Cockcroft-Gault formula, or measured) is less than 30 mL/minute

Hepatic	Omit if ALT and/or AST elevation (>5-8 × ULN) or isolated total bilirubin elevation (>3-5 × ULN). Do not administer tebentafusp until LFTs have improved to ≤ Grade 1. 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 the consultant in charge of the patients care 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 × ULN) with concurrent elevation in total bilirubin (>2 × ULN) and/or INR (>1.5 × ULN, patients not receiving anticoagulants).

Interactions:

- Patients may not receive other additional investigational study drugs, agents, devices, chemotherapy, or any other therapies that may be active against cancer. Palliative radiotherapy or surgery is permitted and bisphosphonates may be given for bone metastases.
- No therapeutic monoclonal antibodies, except for denosumab and tocilizumab, and no immunosuppressive medication may be administered concurrently.
- Corticosteroids and other immunosuppressive agents may interfere with the mechanism of action of tebentafusp.
- Live or attenuated vaccines are prohibited from 28 days prior to the first dose until 30 days after the final dose of the tebentafusp.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Tebentafusp**	**20 micrograms**	IV infusion	Sodium Chloride 0.9% 100mL over 15 minutes
8		**30 micrograms**		
15 and weekly thereafter		**68 micrograms**		

Main toxicities:

Tebentafusp	
Cytokine release syndrome Occurred in 89% of patients in trials	Monitor and treat per local guidance: Immune-Related Adverse Event: Cytokine Release Syndrome
Cytokine mediated: Chills Fatigue Headache Hypotension Nausea Pyrexia Vomiting	Monitor and treat if symptomatic
Skin related: Pruritus Rash	Monitor and treat if symptomatic
Other non-immune adverse events: Hyperbilirubinemia Hypertension Hypophosphatemia Lymphopenia	Monitor and treat if symptomatic

Investigations and treatment plan:

	Pre	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2	Cycle 3	Cycle 4 and ongoing	Ongoing
Informed Consent	X							
Clinical Assessment	X	X			X		X	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	X	X	X	X	Every cycle
CT scan	X							At the end of treatment and if clinically indicated
ECG	X	X	X	X				Repeat on C1D2, C1D9 and C1D16 prior to discharge
Blood pressure measurement	X	X	X	X	X	X	X	Repeat if clinically indicated
Respiratory Rate	X							If clinically indicated
Height and weight recorded	X	X	X	X	X	X	X	Every cycle
Blood glucose	X							Repeat if clinically indicated

Dose Modifications and Toxicity Management:

From a starting tebentafusp dose of 68 micrograms, the dose may be reduced to 54 micrograms for any toxicity requiring dose reduction.

The dose may be reduced further to 50 micrograms for recurrent toxicity.

Patients who require more than two 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.

References:

1. Phase 3 randomized trial comparing tebentafusp with investigator's choice in first-line metastatic uveal melanoma, S. Piperno-Neumann, J. C. Hassel et. al.
2. Protocol - A Managed Access Program which will support patient access to Tebentafusp outside of clinical trials or where Tebentafusp is not yet available, Version 1.0 April 2021, Clinigen Healthcare, Ltd

Circulation/Dissemination

Date added into Q-Pulse	21st April 2022
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
April 2022	1.0	**Michael Cooper – Principal Pharmacist: Medicines Optimisation**	New protocol