BC Cancer Protocol Summary for the Treatment of Metastatic Uveal Melanoma using Tebentafusp

Protocol Code	*USMAVTEB*
Tumour Group	*Skin & Melanoma*
Contact Physician	*Dr. Alison Weppler*

ELIGIBILITY:

Patients must have:

- Human leukocyte antigen (HLA)-A*02:01-positive unresectable or metastatic uveal melanoma,
- BC Cancer "Compassionate Access Program" request approval prior to treatment

Patients should have:

- Good performance status,
- Access to a treatment centre with expertise to manage cytokine release syndrome (CRS)

Notes:

- Inpatient monitoring required for at least the first 3 administrations of tebentafusp (Cycle 1, Days 1, 8, and 15):
  - Patients must be monitored for at least 16 hours after each dose in Cycle 1
  - Responsible provider to assess patient and review labs drawn morning after treatment prior to discharge (on Days 2, 9, 16)
  - Inpatient treatments should be given as early in the morning as possible (most severe adverse events occur within the first 4 to 8 hours following tebentafusp administration)
  - Orders for SCCRS required for patients requiring admission
- Subsequent infusions may be given in ambulatory care setting at provider discretion

EXCLUSIONS:

Patients must not have:

- Active central nervous system metastases (unless asymptomatic and/or stable)

TESTS:

- **Baseline:** CBC & Diff, platelets, creatinine, sodium, potassium, calcium, magnesium, phosphate, total bilirubin, ALT, alkaline phosphatase, LDH, ECG
- **Cycles 1 and 2, prior to each treatment (Days 1, 8 and 15):** CBC & Diff, platelets, creatinine, sodium, potassium, calcium, magnesium, phosphate, ALT, alkaline phosphatase, total bilirubin, LDH
- **Cycle 1, prior to Day 8 and 15:** ECG (optional per provider discretion)
- **Morning after each treatment (Days 2, 9, 16), if patient admitted to hospital during treatment:** CBC & Diff, platelets, creatinine, sodium, potassium, calcium, magnesium, phosphate, ALT, alkaline phosphatase, total bilirubin, LDH
- **Morning after each treatment (Days 2, 9, 16), if patient admitted to hospital during treatment:** ECG (optional per provider discretion)
- **Cycles 3 onwards, prior to each cycle:** CBC & Diff, platelets, creatinine, sodium, potassium, calcium, magnesium, phosphate, ALT, alkaline phosphatase, total bilirubin, LDH

- **Cycles 3 onwards, if clinically indicated:** CBC & Diff, platelets, creatinine, sodium, potassium, calcium, magnesium, phosphate, ALT, alkaline phosphatase, total bilirubin, LDH prior to Days 8 and 15
- **If clinically indicated at any time**: Random glucose

PREMEDICATIONS:

- Antiemetic regimen for low emetogenic protocol (see SCNAUSEA)

If required (for prior Grade 3 or higher CRS):

- dexamethasone 4 mg PO 30 to 60 minutes prior to treatment
- acetaminophen 975 mg PO 30 minutes prior to treatment

If required (for prior Grade 2 or higher skin toxicity):

- diphenhydrAMINE 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible) 30 minutes prior to treatment

HYDRATION:

- NS IV at 50 mL/h continuous infusion during hospital admission (To minimize risk of hypotension related to cytokine release syndrome)

SUPPORTIVE MEDICATIONS:

- Medications related to cytokine release syndrome (CRS) – see Cytokine Release Syndrome Management protocol: SCCRS

If required for rash/pruritus:

- diphenhydrAMINE 25 to 50 mg PO/IV Q4H PRN
- loratadine 10 mg PO Q6H PRN
- montelukast 10 mg PO once PRN for pruritus refractory to antihistamines
- betamethasone valerate 0.1% cream apply topically as needed for rash
- menthol 4% gel apply topically as needed for rash

If required for nausea/vomiting:

- metoclopramide 10 mg PO/IV Q6H PRN
- ondansetron 8 mg PO/IV Q8H PRN

TREATMENT:

Cycle 1: Patient must be admitted to hospital

- Two IVs must be inserted prior to treatment

Drug	Dose	BC Cancer Administration Guideline
tebentafusp	20 mcg on Day 1	IV in 100 mL NS with albumin 5% 0.5 mL over 15 minutes using 0.2 micron in-line filter
	30 mcg on Day 8	
	68 mcg on Day 15	

Due to the risk of treatment-related adverse events, in particular cytokine release syndrome and hypotension, for at least the first cycle of treatment patients must be monitored as an inpatient during the infusion and for at least 16 hours following administration. The infusion

should be given first thing in the morning on day of admission. A physician must be immediately available to respond to emergencies during all inpatient administrations.

Due to the risk of transient hypotension, clinicians should consider reducing or holding antihypertensive medications for 24 hours before and after the first 3 administrations of tebentafusp. Appropriate management of patients, especially those with more severe hypertension, receiving medications that may cause rebound hypertension when abruptly discontinued or those who are on multiple blood pressure medications should be discussed with a cardiology consultant.

Vital signs (including blood pressure, heart rate, temperature and pulse oximetry) must be checked immediately before the start of the infusion, at completion of infusion, 30 and 60 minutes post infusion completion, then every 2 hours (or more frequently if indicated) for the first 12 hours after administration. If there is a drop in blood pressure or clinical evidence of CRS, continue to monitor vital signs according to reaction severity. Otherwise, reduce monitoring to every 4 hours.

See protocol for management of cytokine release syndrome SCCRS for detailed instructions of CRS monitoring and treatment.

If no Grade 2 or worse hypotension during or after Cycle 1 Day 15 dose, subsequent doses may be administered in ambulatory care setting.

Cycle 2 onwards:

- Cycle 2 to be given while patient admitted to hospital if patient experienced Grade 3 or 4 hypotension with any Cycle 1 doses. If no recurrent Grade 2 or higher hypotension, subsequent doses may be administered in ambulatory care setting*
  * See Treatment interruptions, below
- If patient has not reached full dose by Cycle 2 Day 1, ongoing dose escalation should continue in hospital**

Drug	Dose	BC Cancer Administration Guideline
tebentafusp	68 mcg on Days 1, 8 and 15	IV in 100 mL NS with albumin 5% 0.5 mL over 15 minutes using 0.2 micron in-line filter Observe for 1 hour post infusion***

Vital signs (including blood pressure, heart rate, temperature and pulse oximetry) prior to treatment and again at 30 minutes and 60 minutes post infusion completion.

** **If inpatient administration is required, treatment, monitoring and supportive medications to be administered as per Cycle 1.**

*** From Cycle 5 onwards the observation period can be decreased to 30 minutes post infusion, with vital signs prior to treatment and at 30 minutes post infusion completion (if there have been no treatment interruptions greater than 2 weeks).

Repeat every 21 days as long as patient receives clinical benefits.

DOSE MODIFICATIONS:

No dose reductions are recommended for tebentafusp. Dose delays and/or delay in dose escalation may be recommended as per below.

1. **Cytokine Release Syndrome (CRS):** (also see management of cytokine release syndrome protocol: SCCRS)

Severity	Dose
Grade 2	Continue dose escalation as per ramp-up schedule. If persistent Grade 2 CRS (lasting 2 to 3 hours) or recurrent, consider continuing at same dose level (do not escalate until dose is tolerated).
Grade 3	Resume at same dose level (do not escalate until dose is tolerated). Consider corticosteroid premedication at least 30 minutes prior to next dose. If Grade 3 CRS was life-threatening and required multiple vasopressors or intubation/mechanical ventilation, tebentafusp should be permanently discontinued.
Grade 4	Permanently discontinue.

2. **Skin Reactions:**

Severity	Dose
Grade 2	Hold until improves to less than Grade 1 or baseline. Continue dose escalation as per ramp-up schedule. Consider pre-medication with an antihistamine.
Grade 3	Hold until improves to less than Grade 1 or baseline. Resume at same dose level (do not escalate until dose is tolerated) Consider pre-medication with an antihistamine
Grade 4	Permanently discontinue.

3. **Hepatotoxicity:**

- For Grade 3 or 4 hepatotoxicity in the context of CRS, hold treatment until improves to Grade 1 or baseline. Resume at same dose level. Can resume dose escalation if next administration is tolerated.
- For Grade 3 or 4 hepatotoxicity not related to CRS, hold treatment until improves to Grade 1 or baseline. Resume dose escalation or continue at same dose if escalation is completed.
    - Monitor liver enzymes closely. If not improving spontaneously within 2 to 3 days, consider initiation of glucocorticoids.
- Tebentafusp has not been studied in patients with moderate to severe hepatic impairment (total bilirubin greater than 1.5 x ULN)

4. **Renal impairment:**

- No dose adjustments for mild to moderate renal impairment. Tebentafusp has not been studied in patients with severe renal impairment (CrCl less than 30 mL/min).

Treatment Interruptions:

- If treatment interruption of greater than 2 weeks occurs, consider admission to hospital for administration for the subsequent dose after the break.
- If treatment interruption of greater than 2 weeks occurs AND patient has history of Grade 3 or 4 hypotension during first cycle, subsequent dose after the break must be given while patient admitted to hospital.
- If treatment interruption of greater than 4 weeks occurs, consider reducing dose by one step for the subsequent dose after the break, to be given while patient admitted to hospital.
- If inpatient administration is required, treatment, monitoring and supportive medications to be administered as per Cycle 1.

PRECAUTIONS:

1. **Cytokine release syndrome (CRS):** severe CRS has been reported with tebentafusp. The pattern of CRS generally begins 2 to 12 hours following the first 3 doses of tebentafusp and the observed symptoms include fevers, rigors, chills, hypotension (which has been severe in some patients) and hypoxemia. Other commonly reported symptoms, typically mild to moderate, include headache, fatigue, rash or general erythema, pruritus, facial and general edema, myalgias, nausea/vomiting and elevated liver enzymes. Most CRS events occur after the first dose, with decreasing frequency and severity after subsequent doses. Closely monitor patients for signs and symptoms of CRS. CRS may be managed with intravenous fluids, corticosteroids, tocilizumab and other symptomatic measures – see management of cytokine release syndrome protocol SCCRS.
2. **Skin reactions:** including rash, pruritus, erythema, edema, flushing, desquamation, and dry skin are common. Rash is generally erythematous and pruritic, reducing in severity and duration with repeat dosing. Antihistamines and topical or, rarely, systemic corticosteroids may be required depending on severity.
3. **Theoretical risk of viral disease transmission**, due to human albumin component, is extremely remote. A blood transfusion consent must be completed prior to treatment with tebentafusp.

4. Risk of **prolonged QT interval**: Monitor ECG at baseline and as clinically indicated (especially during the first 3 weeks of treatment) for patients at risk of QT prolongation.

Call Dr. Alison Weppler or tumour group delegate at 604-877-6050 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Nathan P, Hassel JC, et al; IMCgp100-202 Investigators. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med. 2021 Sep 23;385 (13):1196-1206.
2. Tebentafusp (Kimmtrak) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies Jan 2023; 3(1): 1-22.