BC Cancer Protocol Summary for Therapy of Multiple Myeloma Using Unfunded Teclistamab

Protocol Code	*UMY0UF (teclistamab)*
Tumour Group	*Myeloma*
Contact Physicians	*Dr. Christopher Venner*

ELIGIBILITY:

Patients must have:

- BC Cancer "Compassionate Access Program" request approval prior to treatment

Patients should have:

- No signs or symptoms of active infection,
- Adequate renal and hepatic function,
- Access to a treatment centre with expertise to manage cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)

Note:

- Inpatient monitoring required for at least the first 3 administrations of teclistamab (Cycle 1: Step-up dose 1, step-up dose 2, and first treatment dose)
- If inpatient treatment:
  - Patients to be monitored for at least 48 hours after each dose in Cycle 1
  - Responsible provider to assess patient and review labs drawn morning after treatment prior to discharge
  - Orders for SCCRS and SCICANS required for patients requiring admission
  - Subsequent doses will be given in ambulatory care setting

TESTS:

- Baseline (required before first treatment): CBC & Diff, platelets, creatinine, sodium, potassium, urea, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): serum protein electrophoresis ***and*** serum free light chain levels, immunoglobulin panel (IgA, IgG, IgM), HCAb, HBsAg, HBsAb, HBcoreAb, beta-2 microglobulin
- Cycle 1:
  - Prior to each dose: CRS and ICANS assessment
  - Prior to each dose: CBC & Diff, platelets, creatinine, sodium, potassium, calcium, magnesium, phosphate, ALT, alkaline phosphatase, total bilirubin, albumin, LDH, vital signs

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- Prior to discharge: CBC & Diff, platelets, creatinine, sodium, potassium, calcium, magnesium, phosphate, ALT, alkaline phosphatase, total bilirubin, albumin, LDH, vital signs

- Cycles 2 onward*:
  - Day 1: CBC & Diff, platelets, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose
  - Days 8, 15, 22 (optional if pre-cycle cytopenias, hypercalcemia, hepatic or renal dysfunction, or steroid-induced diabetes a concern. Results do not have to be available to proceed with treatment. Provider to review results, no dose modifications indicated for mid-cycle bloodwork): CBC & Diff, platelets, creatinine, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, random glucose
- From cycle 3 onwards, every 4 weeks (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis and serum free light chain levels
- From cycle 3 onwards, every 4 weeks (optional, results not mandatory but encouraged prior to each cycle): urine protein electrophoresis, immunoglobulin panel (IgA, IgG, IgM), beta-2 microglobulin
- If clinically indicated: phosphate, magnesium
- *If treatment restarting after treatment interruption and repeat step-up dosing required, see Cycle 1 orders

PREMEDICATIONS:

- Prior to each dose in Cycle 1, when resuming treatment after treatment interruption (if indicated, see Treatment interruptions below), and if CRS of any Grade with previous dose of teclistamab:

60 minutes prior to teclistamab:
- dexamethasone 20 mg PO/IV
- loratadine 20 mg PO (preferred) or diphenhydrAMINE 50 mg PO/IV
- acetaminophen 650 mg to 975 mg PO

SUPPORTIVE MEDICATIONS:

- **Antiviral/Antifungal/Antibacterial Prophylaxis:**
  - Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.
  - Prophylaxis against reactivation of varicella-zoster virus (VZV) and herpes simplex virus (HSV) is recommended prior to initiating. Patients should take valACYclovir 500 mg PO daily
  - Pneumocystis jirovecii (PJP) prophylaxis: Cotrimoxazole 1 DS tablet PO 3 times each week (Monday, Wednesday and Friday) for a minimum of 6 months
  - Antibacterial prophylaxis (Optional in patients with prolonged neutropenia, high risk of intection, history of recurrent infections, or per provider discretion): levoFLOXacin 500 mg PO for 3 months. Prophylaxis may be continued at the discretion of provider

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- Immunoglobulin replacement recommended with IVIG if IgG level less than 5 g/L and history of infection
- **Antiemetics:**
  - Antiemetic protocol for chemotherapy with low emetogenicity (see SCNAUSEA)

TREATMENT:

- Saline lock must be inserted prior to first treatment
- teclistamab will be prescribed as mg/kg, without dose banding as suggested in the product monograph
- Closed system drug transfer devices (e.g., ChemoLock™) cannot be used if dose is less than 1 mL
- teclistamab is available in two different concentrations. Use appropriate concentration based on the Dose preparation table, below
- Dose escalation with step-up dosing schedule mandatory at initiation of treatment and after treatment interruptions if indicated (see Treatment interruptions, below). Do not skip or modify doses. Follow schedule outlined below
- Round step-up dose 1 and step-up dose 2 (0.06 mg/kg and 0.3 mg/kg doses) to one decimal place

Cycle 1:

- Do not administer any doses in Cycle 1 if signs or symptoms of infection regardless of Grade of infection (see Dose Modifications)

Drug	Dose		BC Cancer Administration Guideline
teclistamab	Step-up dose 1	0.06 mg/kg on Day 1	Subcutaneously** (abdomen or thigh)
	Step-up dose 2	0.3 mg/kg on Day 3*	
	First treatment dose	1.5 mg/kg on Day 5*	

* May be given 2 to 7 days after previous dose

** Administer doses greater than 2 mL as two syringes at two separate sites

Dose preparation:

Calculated Dose (mg)	Vial Size (Concentration)
2.1 to 52.9	30 mg (10 mg/mL)
53 to 375	153 mg (90 mg/mL)

For patients admitted to hospital:

- **Observation**: Due to the risk of treatment-related adverse events, in particular CRS, hypotension and ICANS, patients should be monitored as an inpatient during

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administration and for at least 48 hours following each injection for step-up dose 1, step-up dose 2, and the first treatment dose. A physician must be immediately available to respond to emergencies during all inpatient administrations.
- **Vital signs:** (including blood pressure, heart rate, temperature and pulse oximetry) to be measured routinely per hospital policy. If there is a drop in blood pressure or clinical evidence of CRS or ICANS, notify provider immediately and continue to monitor vital signs according to CRS or ICANS protocol.
- 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 teclistamab. 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.
- If no Grade 2 or greater reactions during or after the first three doses (step-up dose 1, step-up dose 2, and first treatment dose), subsequent treatment to be given in ambulatory care setting

Cycle 2 onwards (to start 7 days after first treatment dose):
- To be administered in ambulatory care setting unless adverse reaction with previous dose(s)*

  * See Treatment interruptions, below

Drug	Dose	BC Cancer Administration Guideline
teclistamab	1.5 mg/kg on Days 1, 8, 15, and 22	Subcutaneously* (abdomen or thigh)

* Administer doses greater than 2 mL as two syringes at two separate sites

Repeat every 28 days until disease progression or unacceptable toxicity.

- From Cycle 2 onward, for patients restarting with either step-up dose 1 or step-up dose 2 after treatment interruptions, observation and vital signs as per Cycle 1 requirements
- From Cycle 2 onward, if no treatment interruptions requiring repeat step-up dosing, the observation period can be decreased to 30 minutes post-injection, with vital signs prior to treatment and at 30 minutes post-injection

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DOSE MODIFICATIONS:

No dose reductions are recommended for teclistamab. Dose delays may be recommended as per below.

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

Grade	Management
Grade 1	• Hold until resolution • Manage per SCCRS • Give premedications prior to next dose
Grade 2 or Grade 3 (duration less than 48 hours)	• Hold until resolution • Manage per SCCRS • Give premedications prior to next dose • Consider hospital admission for next dose
Grade 3 (recurrent or duration more than 48 hours) or Grade 4	• Discontinue teclistamab • Manage per SCCRS

2. **Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS):** (also see management of immune effector cell-associated neurotoxicity syndrome protocol: SCICANS)

Grade	Management
1	• Hold until resolution • Manage per SCICANS
2 or 3 (First occurrence)	• Hold until resolution • Manage per SCICANS • Consider hospital admission for next dose
3 (Recurrent) or 4	• Discontinue teclistamab • Manage per per SCICANS

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3. **Infections:**

- Do not give teclistamab in patients with signs or symptoms of active infection, regardless of Grade of infection

4. **Hematological:** (based on pre-cycle lab work)

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Teclistamab Dose
Greater than or equal to 0.5	and	Greater than or equal to 25 without evidence of bleeding	100%
Less than 0.5*	or	Less than 25	• Call physician • Consider G-CSF support • May hold until ANC 0.5 or greater and platelets 25 or greater without bleeding • Consider transfusion support • Restart at 100%
Greater than or equal to 0.5	and	25 to 50 with bleeding	• Call physician • Hold until platelets 25 or greater without bleeding • Restart at 100%
Febrile neutropenia	and	Greater than or equal to 25 without evidence of bleeding	• Call physician • If during Cycle 1, assess for CRS • If beyond Cycle 1, consider G-CSF support • Hold until ANC 1.0 or greater and fever resolves • Restart at 100%

* Avoid filgrastim during periods when patient at risk of CRS. Consider weekly filgrastim if clinically indicated and filgrastim is available. Filgrastim is not covered as a benefit drug by BC Cancer

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5. **Treatment Interruptions:**
   - Treatment schedule and dose may be affected
   - Premedications with dexamethasone, antihistamine and acetaminophen may be required prior to next teclistamab dose when treatment resumed
   - Guidance provided below is intended for patients who tolerated previous dose without toxicity

Last Dose of Teclistamab Administered	Number of Days Since Last Dose Administered	Next Teclistamab Dose When Treatment Resumed
Step-up dose 1 0.06 mg/kg	7 days or less	Proceed with dose escalation: • next scheduled dose: step-up dose 2 (0.3 mg/kg). Premedications required
	More than 7 days	Restart dose escalation: • next scheduled dose: step-up dose 1 (0.06 mg/kg). Premedications required
Step-up dose 2 0.3 mg/kg	7 days or less	Proceed with dose escalation: • next scheduled dose: treatment dose (1.5 mg/kg). Premedications required
	8 to 28 days	Repeat last dose given: • next scheduled dose: step-up dose 2 (0.3 mg/kg). Premedications required
	More than 28 days	Restart dose escalation: • next scheduled dose: step-up dose 1 (0.06 mg/kg). Premedications required
Any treatment dose 1.5 mg/kg	28 days or less	Continue at same dose: • next scheduled dose: treatment dose (1.5 mg/kg). • no premedications required
	More than 28 days	Restart dose escalation: • next scheduled dose: step-up dose 1 (0.06 mg/kg). Premedications required

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PRECAUTIONS:

1. **Cytokine release syndrome (CRS):** has been reported with teclistamab and can recur. The pattern of CRS generally begins 1 to 6 days following the most recent dose of teclistamab and the observed symptoms include fevers, rigors, chills, hypotension (which has been severe in some patients) and hypoxemia. It generally occurs during Cycle 1 only. Other commonly reported symptoms, typically mild to moderate, include headache, facial and general edema, myalgias, nausea/vomiting and elevated liver enzymes. Most CRS events occur during the first 3 doses of teclistamab (during step-up doses and with the first full treatment dose). Follow recommended dose escalation schedule to reduce the risk of CRS. Closely monitor patients for signs and symptoms of CRS. At first sign of CRS, admit patient to hospital for further monitoring if not already admitted. CRS may be managed with intravenous fluids, corticosteroids, tocilizumab and other symptomatic measures – see management of cytokine release syndrome protocol SCCRS.
2. **Neurologic toxicity**, including **immune effector cell-associated neurotoxicity syndrome (ICANS)** and **Guillain-Barré syndrome** can occur during treatment with teclistamab. These can be serious or life-threatening, and can be concurrent with CRS, follow the resolution of CRS, or occur in the absence of CRS. Signs and symptoms include headache, motor dysfunction (e.g., dysgraphia, dysphonia, tremor, hypokinesia and gait disturbance), peripheral neuropathy, and encephalopathy. The most frequently reported neurologic toxicity has been headache. Neurologic toxicity can occur days or weeks after the teclistamab injection and initial symptoms may be subtle. At first sign of ICANS, admit patient to hospital for further monitoring if not already admitted. Neurology consult may be required. Hold teclistamab until neurologic toxicity resolves. Symptoms are managed depending on their severity and whether they occur concurrently with CRS. Permanently discontinue teclistamab for recurrent Grade 3 and Grade 4 events. Due to the potential for ICANS and the risk of reduced consciousness, patients receiving teclistamab should avoid driving or operating heavy machinery for 48 hours after their third dose of initial treatment and until 48 hours after the third dose if re-escalation required for treatment interruption, and if experiencing neurologic symptoms. See management of immune effector cell-associated neurotoxicity protocol- SCICANS.
3. **Local injection site** and **hypersensitivity reactions** are reported during treatment with teclistamab. Local reactions include bruising, cellulitis, discomfort, erythema, hematoma, induration, inflammation, edema, pruritus, rash, and swelling. Systemic reactions have included Grade 1 pyrexia and swollen tongue,
4. **Infections** have been reported in patients treated with teclistamab. These may be severe or life-threatening. Fatalities have been reported. Fever or other evidence of infection must be assessed promptly and treated aggressively. Do not administer step-up dosing schedule if active infection.
5. **Hematologic toxicities:** Teclistamab may cause hypogammablobulinemia, neutropenia, febrile neutropenia, and thrombocytopenia. Monitor for signs of infection and bleeding.
6. **Live vaccines**: Should be discussed with most responsible physician.

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7. **Hepatotoxicity** may occur with teclistamab. Elevated AST, ALT, and total bilirubin have been reported. Liver enzyme elevation may occur with or without concurrent CRS. Hold treatment for Grade 3 hepatotoxicity until Grade 1 or less, and consider discontinuation of teclistamab for Grade 4 hepatotoxicity.
8. **Drug interactions:** The initial release of cytokines associated with teclistamab treatment may suppress CYP450 enzymes. Substrates of CYP450 enzymes with a narrow therapeutic index may require dose adjustment and monitoring for toxicity if given concurrently with teclistamab. The highest risk of interaction is predicted to occur during the teclistamab dose escalation and up to 7 days after the first treatment dose, or during a CRS event.
9. **Hepatitis B Reactivation**: See SCHBV protocol for more details.
10. **Need for irradiated blood products:** Patients receiving an autotransplant require irradiated blood products from 7 days prior to collection to 3 months post transplant (6 months if total body irradiation conditioning) to eliminate the risk of potentially life-threatening transfusion-related graft-versus-host-disease. All other myeloma patients do not require irradiated blood products.

Call Dr. Christopher Venner or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Usmani SZ, Garfall AL, van de Donk NWCJ, et al. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Lancet. 2021 Aug 21;398(10301):665-674.
2. Janssen Inc. TECVAYLI® product monograph. Toronto, Ontario; July 26, 2023
3. Raje N, Anderson K, Einsele H, et al. Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: consensus recommendations from an expert panel. Blood Cancer J. 2023 Aug 1;13(1):116.

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