BC Cancer Interim Protocol for Unfunded Epcoritamab

Protocol Code	*ULY0UF (epcoritamab)*
Tumour Group	*Lymphoma*
Contact Physician	*Dr. Laurie Sehn* *Dr. Alina Gerrie*

ELIGIBILITY:

Patients must have:

- BC Cancer "Compassionate Access Program" request approval prior to treatment.
- Access to a treatment center with expertise to manage cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Patients should have:

- No signs or symptoms of active infection.

Notes:

- Patients must be admitted to hospital for monitoring for at least 24 hours after Cycle 1 Days 1, 8 and 15, unless there is a local plan in place for rapid assessment and intervention of suspected CRS and ICANS following outpatient administration. An adequate local plan must ensure the patient:
  - remains within the proximity of the treating facility for at least 24 hours following Cycle 1 Day 1, 8 and 15
  - is monitored for signs and symptoms of CRS and ICANS
  - is counselled on the signs and symptoms associated with CRS and ICANS and on seeking immediate medical attention should they occur at any time
- Subsequent doses will be given in a private infusion clinic or an ambulatory care setting

TESTS:

- Baseline: CBC & Diff
- Baseline, if clinically indicated: creatinine, sodium, potassium, urea, uric acid, total bilirubin, ALT, alkaline phosphatase, phosphate, 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): HCAb, HBsAg, HbsAb, HbcoreAb
- Prior to each dose: CBC & Diff, vital signs

- If clinically indicated: creatinine, sodium, potassium, phosphate, calcium, magnesium, uric acid, albumin, total bilirubin, ALT, alkaline phosphatase, LDH, glucose

PREMEDICATIONS:

- Cycle 1:
  - 30-60 minutes prior to each dose:
    - dexamethasone 16 mg PO/IV and for 3 consecutive days following each dose
    - diphenhydrAMINE 50 mg PO/IV
    - acetaminophen 650 to 975 mg PO/IV
- Cycle 2 onwards (if patient experienced Grade 2 or 3 CRS with a previous dose):
    - dexamethasone 16 mg PO/IV and for 3 consecutive days following each dose until epcoritamab is given without subsequent CRS of Grade 2 or higher.
- Antiemetic protocol for chemotherapy with low emetogenicity (see SCNAUSEA).

PREHYDRATION:

- Optional IV prehydration with 500 mL NS IV over 30 minutes prior to epcoritamab can be considered, to minimize risk of hypotension related to CRS.

SUPPORTIVE CARE MEDICATIONS:

- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.
- Antiviral prophylaxis against herpes virus infections is recommended prior to initiation of treatment. Patients should take valACYclovir 500 mg PO daily while on treatment and for 3 months following completion of epcoritamab treatment.
- Pneumocystis jirovecii (PJP) prophylaxis: Cotrimoxazole 1 DS tablet PO 3 times each week (Monday, Wednesday and Friday) and for 3 months following completion of epcoritamab treatment.

TREATMENT:

Epcoritamab is available in two different concentrations. Use appropriate concentration based on the table below. Refer to Chemotherapy Preparation and Stability Chart or product monograph for specific mixing instructions.

Dose preparation:

Dose	Vial concentration
0.16 mg	4 mg/0.8 mL
0.8 mg	4 mg/0.8 mL
48 mg	48 mg/0.8 mL

- If patient is admitted for treatment and monitoring, saline lock must be inserted prior to each step-up dose and first full-dose treatment (Cycle 1 Days 1, 8 and 15).
- 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.

Cycle 1

Drug	Treatment Day	Dose	BC Cancer Administration Guideline
epcoritamab	1	Step-up dose 1 0.16 mg	Subcutaneously (lower abdomen or the thigh)
	8	Step-up dose 2 0.8 mg	
	15	First full dose 48 mg	
	22	48 mg	

Monitoring:

All patients should be monitored for treatment-related adverse events, in particular CRS and ICANS, after each administration in Cycle 1 and in subsequent cycles as needed at the discretion of the health care professional. For at least 24 hours following the Step-up and first full treatment dose (Cycle 1, Days 1, 8 and 15), patients should be hospitalized for monitoring, unless there is a local plan in place for rapid assessment and intervention for suspected CRS and ICANS following outpatient administration. An adequate local plan for rapid assessment and intervention must ensure the patient:

- remains within proximity of the treating facility for at least 24 hours after Cycle 1 Day 1, 8 and 15.
- is monitored for signs and symptoms of CRS and ICANS.
- is counselled on the signs and symptoms of CRS and ICANS and to seek immediate medical attention should they occur at any time.

Vital signs: (including blood pressure, heart rate, temperature and pulse oximetry) to be done prior to each dose in cycle 1, and as clinically indicated.

If clinical evidence of CRS or ICANS, notify provider immediately and continue to monitor patient according to SCCRS or SCICANS protocol.

Subsequent cycles to be administered at a private infusion clinic or ambulatory care setting unless treatment interruption requires repeat administration of Step-up dosing or based on clinician discretion in the event of an adverse reaction with prior dose. If repeat administration of Step-up dosing is required, monitor patient as per Cycle 1 requirements.

Cycle 2 and 3

Drug	Dose	BC Cancer Administration Guideline
epcoritamab	48 mg on Days 1, 8, 15, and 22	Subcutaneously (lower abdomen or the thigh)

Monitoring: If clinical evidence of CRS or ICANS, notify provider immediately and continue to monitor patient according to SCCRS or SCICANS protocol.

Vital signs as clinically indicated for Cycle 2 onwards.

Cycles 4 to 9

Drug	Dose	BC Cancer Administration Guideline
epcoritamab	48 mg on Days 1 and 15	Subcutaneously (lower abdomen or the thigh)

Cycles 10 onwards

Drug	Dose	BC Cancer Administration Guideline
epcoritamab	48 mg on Day 1	Subcutaneously (lower abdomen or the thigh)

1 cycle = 28 days. Continue treatment until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

Dose reductions are not recommended for epcoritamab. Withhold drug to manage adverse events**.**

1. **Cytokine Release Syndrome (CRS):**

- Management of CRS may require either temporary delay or discontinuation of epcoritamab, based on severity.
- See management of cytokine release syndrome protocol (SCCRS) for detailed instructions of CRS monitoring and treatment.
- If a patient experiences Grade 2 or greater CRS, inpatient treatment may be considered for the subsequent doses at the discretion of the treating physician.

Grade	Management
Grade 1 to 3	• Hold until resolution of CRS. • Manage per SCCRS. • If resolved prior to next scheduled dose, continue with next treatment as planned. • If treatment interruption, resume treatment as per treatment interruption section below.
Grade 4	• Discontinue epcoritamab. • Manage per SCCRS.

2. **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS):** see management of ICANS protocol (SCICANS)

Grade	Management
Grade 1 to 2	• Hold until resolution of ICANS. • Manage per SCICANS. • If resolved prior to next scheduled dose, continue with next treatment as planned. • If treatment interruption, resume treatment as per treatment interruption section below.
Grade 3 (first occurrence)	• Hold until resolution of ICANS. • Manage per SCICANS. • If resolved prior to next scheduled dose, continue with next treatment as planned. • If treatment interruption, resume treatment as per treatment interruption section below.
Grade 3 (recurrent) or Grade 4	• Discontinue epcoritamab. • Manage per SCICANS.

3. **Infections:**

- Withhold epcoritamab in patients with active infection, until the infection fully resolves.
- Resume treatment as per treatment interruption section below.

4. **Hematology:**

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Epcoritamab Dose
Greater than or equal to 0.5	and	Greater than or equal to 50	100%
Less than 0.5	and/ or	Less than 50	Withhold epcoritamab until ANC is greater than or equal to 0.5 and platelets are greater than or equal to 50 then restart treatment as per table below (unless related to lymphoma involvement).

5. **Treatment Interruptions:**

- Treatment schedule and dose may be affected. See below for recommendations regarding management of treatment interruptions.
- Administer premedications as per cycle 1 if restarting step-up dosing, and monitor patients accordingly.

Last Dose Administered	Duration Since Last Dose	Action for next dose
0.16 mg	More than 8 days	▪ Repeat 0.16 mg, then administer 0.8 mg the following week, followed by two weekly doses of 48 mg. ▪ Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.
0.8 mg	14 days or less	▪ Administer 48 mg. ▪ Then resume the recommended dosage schedule.
	More than 14 days	▪ Repeat 0.16 mg, then administer 0.8 mg the following week, followed by two weekly doses of 48 mg. ▪ Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.
48 mg	6 weeks or less	▪ Administer 48 mg. ▪ Then resume the recommended dosage schedule.
	More than 6 weeks	▪ Repeat 0.16 mg, then administer 0.8 mg the following week, followed by two weekly doses of 48 mg. ▪ Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.

PRECAUTIONS:

1. **Cytokine release syndrome (CRS)** has been reported with epcoritamab and can recur with initial doses. 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, facial and general edema, myalgias, nausea/vomiting and elevated liver enzymes. Median time of onset from the most recent dose is 2 days, but may occur up to 11 days after most recent dose. Most CRS events occur in Cycle 1 and are associated with the first full dose of epcoritamab. Unless a local plan is in place for rapid assessment and intervention of suspected CRS and ICANS following outpatient administration, all patients should be admitted for the ramp up doses and first full dose. Transition to the outpatient setting should not occur unless a full dose of drug is delivered without evidence of CRS or ICANS. 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 acetaminophen, intravenous fluids, tocilizumab, corticosteroids, and other symptomatic measures – see management of cytokine release syndrome protocol SCCRS. If patients present with symptomss suggestive of CRS after Cycle 1, especially after successful full dose free of CRS or ICANS, other causes such as infection should be thoroughly investigated and ruled out prior to concluding CRS is the cause.
2. **Neurologic toxicity**, including **immune effector cell-associated neurotoxicity syndrome (ICANS)** can occur during treatment with epcoritamab. This 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 epcoritamab 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 epcoritamab until neurologic toxicity resolves. Symptoms are managed depending on their severity and whether they occur concurrently with CRS. Permanently discontinue epcoritamab for recurrent Grade 3 or any Grade 4 events. Patients experiencing reduced consciousness or any symptoms that might affect their ability to drive or use machines, should refrain from driving or operating heavy machinery until symptoms resolve. See management of immune effector cell-associated neurotoxicity protocol, SCICANS.
3. **Tumour Lysis Syndrome (TLS):** TLS has been reported in patients treated with epcoritamab. Patients considered to be at increased risk for TLS should receive hydration and prophylactic treatment with uric acid lowering agents. Patients should be monitored closely for signs and symptoms of TLS, especially patients

with high tumour burden, rapidly proliferative tumours or reduced renal function. Monitor blood chemistries regularly and manage abnormalities promptly.

4. **Use in Renal Impairment:** No clinically significant differences in pharmacokinetics were observed for mild to moderate renal impairment. The effect of severe renal impairment are unknown and no dose recommendations can be made.
5. **Use in Hepatic Impairment:** No clinically significant differences in pharmacokinetics were observed for mild hepatic impairment. The safety and efficacy of epcoritamab in moderate to severe hepatic impairment have not been studied.
6. **Infections** have been reported in patients treated with epcoritamab. 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 epcoritamab in patients with active systemic infections. Prophylaxis against viral infections and PJP should be administered as per above.
7. **Drug Interactions:** The initial release of cytokines associated with the start of epcoritamab treatment could suppress CYP450 enzymes, resulting in increased exposure of CYP substrates. Increased exposure to CYP substrates is predicted to occur. On initiation of epcoritamab in patients being treated with CYP450 ssubstrates should be considered.
8. **Hepatitis B Reactivation:** Very high risk. See SCHBV protocol for more details.
9. **Vaccination:** Patients should not receive live or live attenuated vaccines within 4 weeks of starting treatment and at any point during treatment.

References:

1. AbbVie Corporation. EPKINLY® product monograph. St-Laurent, Quebec; October 13, 2023