BC Cancer Protocol Summary for Treatment of Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma using Zanubrutinib

Protocol Code	*LYCLLZANU*
Tumour Group	*Lymphoma*
Contact Physician	*Dr. Alina Gerrie*

ELIGIBILITY:

Patients must have:

- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), and
- One of the following indications:
  - First line treatment (no prior therapy):
    - High-risk disease (e.g., chromosome 17p deletion, TP53 mutation and/or unmutated immunoglobulin heavy chain variable region [IGHV] status), or
    - Ineligible for FCR, defined as patients over 65 years of age, and/or a strong clinical reason that the patient is ineligible for FCR,

  OR

  - Relapsed or refractory treatment (previously received at least one prior systemic therapy), regardless of risk group, and symptomatic, requiring therapy

Patients should have:

- Good performance status

Notes:

- First line treatment:
  - patients discontinuing iBRUtinib (LYFIBRU) or acalabrutinib (LYFACAL) due to intolerance may switch to zanubrutinib (LYCLLZANU). Switching after progression is not funded.
- Relapsed/refractory treatment:
  - Patients are eligible to receive one of: idelalisib with riTUXimab (LYIDELAR) OR iBRUtinib (LYIBRU) OR acalabrutinib (LYACAL) OR zanubrutinib (LYCLLZANU) in the relapsed/refractory setting. LYIDELAR is not funded as a sequential treatment option for patients who have progressed on iBRUtinib, acalabrutinib, or zanubrutinb, except on a case by case basis as a bridge to allogeneic transplant or other cellular therapy.
  - If acalabrutinib (LYACAL) or iBRUtinib (LYIBRU) is discontinued for any reason other than progression, LYCLLZANU may be considered for subsequent treatment regardless of time since discontinuation. Switching after progression is not funded.

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EXCLUSIONS:

Patients must not have:

- Prior progression on BTK inhibitor,
- Richter's transformation

CAUTIONS:

- Patients at high risk for bleeding complications,
- Cardiac risk factors including history of hypertension, diabetes mellitus, cardiac arrhythmia, cardiac failure

TESTS:

- Baseline (required before first treatment): CBC & Diff, platelets, creatinine, total bilirubin, ALT, PTT, INR
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBsAb, HBcoreAb
- Baseline if clinically indicated: Albumin, calcium, uric acid, potassium, phosphate, random glucose, LDH, ECG, MUGA scan or echocardiogram
- Each time seen by physician: CBC & Diff, platelets, total bilirubin, ALT, blood pressure
- If clinically indicated: Albumin, calcium, uric acid, potassium, phosphate, random glucose, creatinine, LDH, PTT, INR, ECG, MUGA scan or echocardiogram

PREMEDICATIONS:

- None

SUPPORTIVE MEDICATIONS:

- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
zanubrutinib	160 mg twice daily* (Total daily dose = 320 mg)	PO

* May be given as 320 mg once daily

Continuously until disease progression or unacceptable toxicity.

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DOSE MODIFICATIONS:

Toxicity	Zanubrutinib dose
*Neutropenia Grade 4 lasting more than 10 consecutive days (ANC less than 0.5 x 10^9/L) Or Febrile neutropenia Grade 3 (ANC less than 1.0 x 10^9/L with a single temperature of greater than 38.3 degrees C or a sustained temperature of greater than or equal to 38 degrees C for more than one hour)	Hold until ANC greater than or equal to 1.5 x 10^9/L or baseline, then restart at dose indicated below
*Grade 4 thrombocytopenia lasting more than 10 consecutive days (platelets less than 25 x 10^9/L) or Grade 3 thrombocytopenia with significant bleeding (platelets 25 to less than 50 x 10^9/L)	Hold until platelets greater than or equal to 75 x 10^9/L or baseline, then restart at dose indicated below
Non-hematological toxicity greater than or equal to Grade 3 (severe or life-threatening)	Hold until toxicity less than or equal to Grade 1 or baseline, restart at dose indicated below. Evaluate benefits and risks before resuming at the same dose following grade 4 non-hematological toxicity

* No dose reduction if decreased counts are due to disease

Toxicity	Zanubrutinib dose
Cardiac arrhythmias	Manage appropriately as clinically indicated. Evaluate benefits and risks of continued treatment
Intracranial haemorrhage (any grade)	Discontinue

Toxicity Occurrence	Dose Modification After Recovery
1st	Restart at 160 mg twice daily or 320 mg once daily
2nd	Restart at 80 mg twice daily or 160 mg once daily
3rd	Restart at 80 mg once daily
4th	Discontinue

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PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Hemorrhagic events:** Minor hemorrhagic events including bruising, epistaxis and petechiae occur in approximately half of the patients treated with zanubrutinib. Major hemorrhagic events (serious or Grade 3 or higher bleeding) occur in 1 to 4% of patients**.** Use with caution in patients taking anticoagulants or medications that inhibit platelet function. Hold treatment for 3 to 7 days pre- and post-surgery; reinitiate post-surgery based on the risk of bleeding.
3. **Infections**: Bacterial, viral, fungal, and opportunistic infections are frequently reported with zanubrutinib. Approximately 20% of reported infections are associated with concurrent neutropenia. Fatal infections have been reported in 2.5% of patients. Consider prophylaxis in patients who are at increased risk for infection and manage infections appropriately.
4. **Second primary malignancies**: Serious and fatal malignancies have been reported in patients being treated with zanubrutinib. Skin cancer, the most frequently occurring second primary malignancy, was reported in 9% of patients and can include basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. Monitor for the appearance of suspicious skin lesions, and advise patients on appropriate sun protection measures.
5. **Drug Interactions:** Zanubrutinib is a substrate of CYP3A4. Concomitant therapy with strong or moderate CYP 3A4 inhibitors may increase zanubrutinib exposure; avoid if possible. Zanubrutinib dose reduction for concurrent use may be necessary. Concomitant use of zanubrutinib with strong CYP 3A4 inducer may decrease zanubrutinib exposure; avoid if possible. Refer to Cancer Drug Manual for more information, including dose reduction guidance for common medication interactions.
6. **Hypertension** has been reported in patients taking Bruton's tyrosine kinase (BTK) inhibitors. Blood pressure should be checked at each visit and treated if it develops. Hypertension increases the risk of cardiac complications with BTK inhibitor treatment.
7. **Atrial fibrillation and atrial flutter** are reported with zanubrutinib use; risk may be increased in patients with cardiac risk factors, hypertension, or acute infection.
8. **Lymphocytosis:** Has been reported upon treatment initiation with zanubrutinib. The median time to onset of lymphocytosis in studies was 4 weeks and the median duration of lymphocytosis was 8 weeks. Patients with asymptomatic lymphocytosis should continue treatment with zanubrutinib.
9. **Interstitial Lung Disease (ILD):** has been reported in patients during treatment with zanubrutinib. Monitor patients for signs and symptoms of ILD. Hold treatment for suspected ILD. Discontinue treatment if ILD is confirmed.
10. **Hepatic Impairment:** Reduce zanubrutinib dose to 80 mg PO BID for severe hepatic impairment. Monitor for adverse reactions. No dose adjustment required for mild or moderate hepatic impairment. Monitor for toxicity.
11. **Hepatitis B Reactivation**: See SCHBV protocol for more details.

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

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References:

1. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Lancet Oncol. 2022 Aug;23(8):1031-1043.
2. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med. 2023 Jan 26;388(4):319-332.
3. CADTH Reimbursement Review Zanubrutinib (Brukinsa). Canadian Journal of Health Technologies September 2023 Volume 3 Issue 9
4. CADTH Provisional Funding Algorithm: Chronic lymphocytic leukemia. October 2023

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