

BC Cancer Protocol Summary for Treatment of Waldenström Macroglobulinemia or Lymphoplasmacytic Lymphoma (LPL) using Zanubrutinib

Protocol Code

ULYWMZANU

Tumour Group

Lymphoma

Contact Physician

Dr. Alina Gerrie

ELIGIBILITY:

Patients must have:

- Relapsed or refractory Waldenström macroglobulinemia (WM) or lymphoplasmacytic lymphoma (LPL),
- Symptomatic disease requiring therapy,
- Received at least one prior systemic therapy, and
- BC Cancer “Compassionate Access Program” request approval prior to treatment

Patients should have:

- ECOG 0 to 2

Note: if other Bruton tyrosine kinase (BTK) inhibitor is discontinued for any reason other than progression, ULYZANU may be considered for subsequent treatment regardless of time since prior BTK inhibitor discontinuation

EXCLUSIONS:

Patients must not have:

- Disease transformation
- Prior progression on BTK inhibitor

CAUTION:

- Patients at high risk for bleeding complications

TESTS:

- Baseline (required before first treatment): CBC & Diff, 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, [serum protein electrophoresis](#), [serum free light chain levels](#), [immunoglobulin panel \(IgA, IgG, IgM\)](#)
- Each time seen by physician: CBC & Diff, total bilirubin, ALT, [serum protein electrophoresis](#), [serum free light chain levels](#), [immunoglobulin panel \(IgA, IgG, IgM\)](#)
- 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 start 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.

DOSE MODIFICATIONS:

Toxicity	Zanubrutinib dose
*Neutropenia Grade 4 lasting more than 10 consecutive days (ANC less than $0.5 \times 10^9/L$) Or Febrile neutropenia Grade 3 (ANC less than $1 \times 10^9/L$ 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 $1.5 \times 10^9/L$ or baseline, then restart at dose indicated below
*Grade 4 thrombocytopenia lasting more than 10 consecutive days (platelets less than $25 \times 10^9/L$) or Grade 3 thrombocytopenia with significant bleeding (platelets 25 to less than $50 \times 10^9/L$)	Hold until platelets greater than or equal to $75 \times 10^9/L$ 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
Cardiac arrhythmias	Manage appropriately as clinically indicated. Evaluate benefits and risks of continued treatment
Intracranial haemorrhage (any grade)	Discontinue

*No dose reduction if decreased counts are due to disease

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

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; reinstitute 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. **Atrial fibrillation and atrial flutter** are reported with zanubrutinib use; risk may be increased in patients with cardiac risk factors, hypertension, or acute infection.
7. **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.
8. **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.
9. **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.
10. **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.

References:

1. Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood*. 2019 Sep 12;134(11):851-859.
2. Trotman J, Opat S, Gottlieb D, et al. Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: 3 years of follow-up. *Blood*. 2020 Oct 29;136(18):2027-2037.
3. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood*. 2020 Oct 29;136(18):2038-2050.
4. Dimopoulos M, Sanz RG, Lee HP, et al. Zanubrutinib for the treatment of MYD88 wild-type Waldenström macroglobulinemia: a substudy of the phase 3 ASPEN trial. *Blood Adv*. 2020 Dec 8;4(23):6009-6018.