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

Protocol Code	*ULYZANU*
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, platelets, creatinine, bilirubin, ALT, IgM level, 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, HBcoreAb
- Each time seen by physician: CBC & diff, platelets, bilirubin, ALT
- If clinically indicated: albumin, calcium, uric acid, potassium, phosphate, random glucose, creatinine, LDH, IgM level, PTT, INR, ECG, MUGA scan or echocardiogram

PREMEDICATIONS:

- None

SUPPORTIVE MEDICATIONS:

If HBsAg or HBcoreAb positive, start hepatitis B prophylaxis as per current guidelines

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 x 10^9/L) Or Febrile neutropenia Grade 3 (ANC less than 1 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
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 occurence	Dose Modification After Recovery
1st	Restart at 320 mg once daily or 160 mg twice daily
2nd	Restart at 160 mg once daily or 80 mg twice daily
3rd	Restart at 80 mg once daily
4th	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; 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. **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**: All lymphoma patients should be tested for both HBsAg and HBcAb. If either test is positive, such patients should be treated with hepatitis B prophylaxis according to current guidelines. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every three months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.

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.