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

Protocol Code	*ULYWMIBRU*
Tumour Group	*Lymphoma*
Contact Physicians	*LY Systemic therapy*

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:

- Good performance status

Notes:

- iBRUtinib is associated with a higher risk of cardiac toxicities compared to zanubrutinib
- Patients are eligible to receive either zanubrutinib (ULYWMZANU) or iBRUtinib (ULYWMIBRU) in the relapsed/refractory setting. Sequential use is not funded.
- If zanubrutinib (ULYWMZANU) is discontinued for any reason other than progression, LYIBRU may be considered for subsequent treatment regardless of time since discontinuation. Switching after progression is not funded.

EXCLUSION:

Patients must not have:

- Disease transformation
- Previous progression on BTK inhibitor

CAUTIONS:

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

TESTS:

- Baseline (required before first treatment): CBC & Diff, creatinine, total bilirubin, ALT, PT, 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)
- Baseline if clinically indicated: ECG, MUGA scan or echocardiogram
- Each time seen by physician: CBC & Diff, total bilirubin, ALT, serum protein electrophoresis, serum free light chain levels, immunoglobulin panel (IgA, IgG, IgM), blood pressure
- If clinically indicated: creatinine, PT, PTT, INR, ECG, MUGA scan or echocardiogram
- If clinically indicated: HBV viral load (see protocol SCHBV)

PREMEDICATIONS:

- None

SUPPORTIVE MEDICATIONS:

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

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
iBRUtinib	420 mg daily	PO

Continuously until disease progression or unacceptable toxicity

DOSE MODIFICATIONS:

1. Myelosuppression:

Toxicity	iBRUtinib Dose
*Neutropenia Grade 4 (ANC less than 0.5 x 10^9/L) or Grade 3 neutropenia (ANC 0.5-1.0 x 10^9/L) associated with an infection or fever 38.5°C	Hold until ANC greater than or equal to 1.0, restart at dose indicated below
*Grade 4 thrombocytopenia (platelets less than 25 x 10^9/L) or Grade 3 (platelets less than 50 x 10^9/L) with bleeding	Hold until platelets greater than or equal to 50, restart at dose indicated below
Nonhematological toxicity greater than or equal to Grade 3	Hold until improvement to grade 1 toxicity or baseline, restart at dose indicated below

*No dose reduction if decreased counts are due to disease

Toxicity Occurrence	Dose Modification After Recovery
1st	Restart at 420 mg daily
2nd	Restart at 280 mg daily
3rd	Restart at 140 mg daily
4th	Discontinue

2. Cardiac Toxicities:

Toxicity	Recommended iBRUtinib dose
Grade 2 cardiac failure	First occurrence: Hold until improvement to grade 1 or baseline. Restart at 280 mg PO daily
	Second occurrence: Hold until improvement to grade 1 or baseline. Restart at 140 mg PO daily
	Third occurrence: Discontinue iBRUtinib
Grade 3 cardiac arrhythmias	First occurrence: Hold until improvement to grade 1 or baseline. Restart at 280 mg PO daily
	Second occurrence: discontinue iBRUtinib
Grade 3 or 4 cardiac failure or Grade 4 cardiac arrhythmias	First occurrence: discontinue iBRUtinib

Grading of Adverse Cardiac Events*

Adverse Event		Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Failure		Asymptomatic with laboratory (e.g., BNP [BNatriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
Cardiac Arrhythmias	**Atrial Fibrillation or Atrial Flutter**	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated; device (e.g., pacemaker); ablation; new onset	Life-threatening consequences; embolus requiring urgent intervention
	Ventricular Arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Urgent intervention indicated	Life-threatening consequences; hemodynamic compromise

*Table not exhaustive. See CTCAE v5.0 for additional information, including for grading of other arrhythmias not listed here.

3. Hepatic Impairment:

Hepatic Impairment	Recommended Dose
Mild (Child-Pugh Class A)	140 mg PO daily; monitor patient for signs of toxicity
Moderate or severe (Child-Pugh Class B or C)	not recommended; hepatic impairment is associated with coagulopathy and may increase the risk of bleeding

3. Renal Impairment:

- No adjustment recommended in mild or moderate renal impairment; no information found for severe renal impairment.

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 iBRUtinib. Major hemorrhagic events including subdural hematoma, gastrointestinal bleeding, hematuria and post-procedural bleeding occur in 3% of patients**.** Use with caution in patients taking anticoagulants or medications that inhibit platelet function. Hold treatment for 3-7 days pre- and post-surgery; reinitiate post-surgery based on the risk of bleeding.
3. **CYP3A4 substrate:** Concomitant therapy with strong or moderate CYP 3A inhibitors may increase iBRUtinib exposure; avoid if possible. iBRUtinib dose reduction for concurrent use may be necessary. Concomitant use of iBRUtinib with strong CYP 3A inducer may decrease iBRUtinib exposure; avoid if possible.
4. **Elderly patients:** patients over 65 yrs of age experience more cardiac events (atrial fibrillation, hypertension), infection (pneumonia, cellulitis), gastrointestinal events (diarrhea, dehydration), as well as a higher frequency of grade 3 or greater adverse effects.
5. **Cardiac failure:** evaluate cardiac risk at baseline and monitor for signs of deterioration during treatment with iBRUtinib. Hold iBRUtinib as indicated in dose modifications above and evaluate with echocardiogram for new onset or worsening cardiac failure. Consider risk vs benefit prior to restarting at reduced dose.
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. **Cardiac arrhythmias including atrial fibrillation**: baseline ECG recommended for patients with cardiac risk factors. ECG is recommended in patients who develop arrhythmic symptoms including palpitations and lightheadedness or a new onset of dyspnea. If atrial fibrillation persists, evaluate the risk vs. benefit of continuing treatment. iBRUtinib dose reduction is recommended for patients who develop cardiac arrhythmias or who have worsening symptoms while taking iBRUtinib.
8. **Lymphocytosis:** Has been reported, usually occurring within the first few weeks of therapy and resolving by 8-23 weeks. Possibly related to the inhibition of BTK-mediated cellular homing and adhesion.
9. **Hepatitis B Reactivation**: See SCHBV protocol for more details.

Contact the LY Systemic Therapy physician at your regional cancer centre or LY Systemic Therapy Chair with any problems or questions regarding this treatment program.

References:

1. Ibrutinib (Imbruvica) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies 2024; 4(1): 1-27.
2. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia. N Engl. J Med. 2018 Jun 21;378(25):2399-2410.
3. Buske C, Tedeschi A, Trotman J, et al. Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study. J Clin Oncol. 2022 Jan 1;40(1):52-62
4. Trotman, J, Buske C, Tedeschi A et al. Single-Agent Ibrutinib for Rituximab-Refractory Waldenström Macroglobulinemia: Final Analysis of the Substudy of the Phase III Innovate™ Trial. Clin Cancer Res. 2021 Nov 1;27(21):5793-5800.
5. 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.