

BC Cancer Protocol Summary for Treatment of Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma Using iBRUtinib

Protocol Code

ULYFIBRU

Tumour Group

Lymphoma

Contact Physician

Dr. Laurie Sehn

ELIGIBILITY:

- Patients must have chronic lymphocytic leukemia or small lymphocytic lymphoma with no prior therapy, and:
 - With high risk disease (e.g chromosome 17 p deletion 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.
- AST/ALT less than 3 x ULN
- A Compassionate Access Program (CAP) approval is required prior to the initiation of treatment (please refer to <https://cap.phsa.ca/>).

** Patients are eligible to receive either idelalisib with rituximab (LYIDELAR) OR iBRUtinib (LYIBRU) in the relapsed/refractory setting. LYIDELAR is not funded as a sequential treatment option for patients who have progressed on iBRUtinib, except as a bridge to allogeneic transplant in patients who have received first-line iBRUtinib for 17p deletion (ULYFIBRU) or high risk disease.*

TESTS:

- Baseline (required before first treatment): CBC & diff, platelets, creatinine, 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, HBcoreAb
- Each time seen by physician: CBC & diff, bilirubin, ALT
- If clinically indicated: creatinine, PT, PTT, INR, ECG

PREMEDICATIONS:

- None

SUPPORTIVE MEDICATIONS:

If HBsAg or HBcoreAb positive, start lamivudine 100 mg PO daily for the duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
iBRUtinib	420 mg daily	PO

Continuously until disease progression or unacceptable toxicity

DOSE MODIFICATIONS:

Toxicity occurrence	CLL dose modification after recovery
1st	Restart at 420 mg daily
2 nd	Restart at 280 mg daily
3rd	Restart at 140 mg daily
4th	Discontinue

1. Myelosuppression:

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

*No dose reduction if decreased counts are due to disease

2. Hepatic Impairment:

Hepatic impairment	Recommended dose
Mild (<u>Child-Pugh Class A</u>)	140 mg PO daily; monitor patient for signs of toxicity
Moderate or severe (<u>Child-Pugh Class B or C</u>)	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. **Hyperuricemia and tumour lysis syndrome:** Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely. See BC Cancer Drug Manual iBRUtinib Drug Monograph for more information.
3. **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; reinstitute post-surgery based on the risk of bleeding.
4. **CYP3A4 substrate:** Concomitant therapy with strong or moderate CYP 3A inhibitors may increase iBRUtinib exposure; avoid if possible. Concomitant use of iBRUtinib with strong CYP 3A inducer may decrease iBRUtinib exposure; avoid if possible.
5. **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.
6. **Persistent atrial fibrillation:** 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 and consider a dose reduction.
7. **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.
8. **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 lamivudine during chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcAb positive. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two 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. Laurie Sehn or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol* 2013;31:88-94.
2. Gerrie AS, Toze CL, Ramadan KM, et al. Fludarabine and rituximab as initial therapy for symptomatic chronic lymphocytic leukemia or small lymphocytic lymphoma: population-based experience matches clinical trials. *Blood* 2009;114:abstr 2363.
3. Tsimberidou AM, Keating MJ. Treatment of fludarabine-refractory chronic lymphocytic leukemia. *Cancer* 2009;115:2824-36.
4. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2013;369:32-42.
5. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphocytic leukemia. *N Engl J Med* 2014;371:213-23.