BC Cancer Protocol Summary for Treatment of Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma using Acalabrutinib

Protocol Code	*ULYFACAL*
Tumour Group	*Lymphoma*
Contact Physician	*Dr. Alina Gerrie* *Dr. Laurie Sehn*

ELIGIBILITY:
Patients must have:
- Chronic lymphocytic leukemia or small lymphocytic lymphoma with no prior therapy, and:
  - High risk disease (eg. 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.
- A BC Cancer Compassionate Access Program (CAP) approval prior to the initiation of treatment

Patients should have:
- Adequate renal and hepatic function

Note:
Patients discontinuing iBRUtinib (ULYFIBRU) due to intolerance may switch to ULYFACAL, CAP request is required.

TESTS:

- Baseline (required before first treatment): CBC & differential, platelets, creatinine, bilirubin, ALT
- 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 & differential, platelets, 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
acalabrutinib	100 mg twice daily	PO

Continuously until disease progression or unacceptable toxicity

DOSE MODIFICATIONS:

Toxicity occurrence	Dose modification after recovery
1st	Restart at 100 mg twice daily
2nd	Restart at 100 mg twice daily
3rd	Restart at 100 mg once daily
4th	Discontinue

1. Myelosuppression:

Toxicity	Acalabrutinib dose
*Grade 4 neutropenia (ANC less than 0.5 x 10^9/L) lasting longer than 7 days	Hold until ANC greater than or equal to 1.5 x 10^9/L or baseline level, then restart at dose indicated above
*Grade 4 thrombocytopenia (platelets less than 25 x 10^9/L) or Grade 3 (platelets less than 50 x 10^9/L) with significant bleeding	Hold until platelets greater than or equal to 75 x 10^9/L or baseline level, then restart at dose indicated above
Non-hematological 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:
No adjustment recommended in mild or moderate hepatic impairment. Avoid use in patients with severe hepatic impairment (Child-Pugh C or bilirubin >3 x ULN regardless of AST/ALT).

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 acalabrutinib. Major hemorrhagic events (serious or Grade 3 or higher 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 acalabrutinib exposure; avoid if possible. Concomitant use of acalabrutinib with strong CYP 3A inducer may decrease acalabrutinib exposure; avoid if possible. If concomitant use cannot be avoided, dose modification may be required.
4. **Atrial fibrillation/flutter**: Risk may be increased in patients with cardiac risk factors, preexisting cardiovascular disease, hypertension, previous history of atrial fibrillation, and infection/pneumonia. ECG is recommended in patients who develop arrhythmic symptoms including palpitations and lightheadedness or a new onset of dyspnea.
5. **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.
6. **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 HBcoreAb positive. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA 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. Alina Gerrie, 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. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet 2020;395:1278-91.
2. AstraZeneca Canada Inc. CALQUENCE® product monograph. Mississauga, Ontario; 28 November 2019.