BCCA Protocol Summary for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma Using iBRUtinib

**Protocol Code**

ULYIBRU

**Tumour Group**

Lymphoma

**Contact Physician**

Dr. Laurie Sehn

**ELIGIBILITY:**

- Chronic lymphocytic leukemia or small lymphocytic lymphoma with or without chromosome 17 p deletion, who have received at least one prior therapy and are considered inappropriate for treatment or retreatment with a fludarabine-based regimen including short progression-free interval after previous treatment*
- 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/](https://cap.phsa.ca/)).

*Patients are eligible to receive either idelalisib with riTUXimab (ULYIDELAR) OR iBRUtinib (ULYIBRU) in the relapsed/refractory setting. ULYIDELAR 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, AST, 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, HBoCreAb
- Each time seen by physician: CBC & diff, bilirubin, AST, ALT
- If clinically indicated: creatinine, PT, PTT, INR, ECG

**PREMEDICATIONS:**

- None

**SUPPORTIVE MEDICATIONS:**

If HBsAg or HBoCreAb positive, start lamivudine 100 mg/day PO for the duration of chemotherapy and for six months afterwards.

**TREATMENT:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>iBRUtinib</td>
<td>420 mg daily</td>
<td>PO</td>
</tr>
</tbody>
</table>

Continuously until disease progression or unacceptable toxicity
DOSE MODIFICATIONS:

<table>
<thead>
<tr>
<th>Toxicity occurrence</th>
<th>CLL dose modification after recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Restart at 420 mg daily</td>
</tr>
<tr>
<td>2nd</td>
<td>Restart at 280 mg daily</td>
</tr>
<tr>
<td>3rd</td>
<td>Restart at 140 mg daily</td>
</tr>
<tr>
<td>4th</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

1. Myelosuppression:

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>iBRUtinib dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>*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</td>
<td>Hold until ANC greater than or equal to 1, restart at dose indicated above</td>
</tr>
<tr>
<td>*Grade 4 thrombocytopenia (platelets less than 25 x 10^9/L) or Grade 3 (platelets less than 50 x 10^9/L) with bleeding</td>
<td>Hold until platelets greater than or equal to 50 restart at dose indicated above</td>
</tr>
<tr>
<td>Nonhematological toxicity greater than or equal to Grade 3</td>
<td>Hold until improvement to grade 1 toxicity or baseline, restart at dose indicated above</td>
</tr>
</tbody>
</table>

*No dose reduction if decreased counts are due to disease

2. Hepatic Impairment:

<table>
<thead>
<tr>
<th>Hepatic impairment</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (Child-Pugh Class A)</td>
<td>140 mg PO daily; monitor patient for signs of toxicity</td>
</tr>
<tr>
<td>Moderate or severe (Child-Pugh Class B or C)</td>
<td>not recommended; hepatic impairment is associated with coagulopathy and may increase the risk of bleeding</td>
</tr>
</tbody>
</table>

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 Agency 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; reinitiate 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, cellulitus), 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 HBeAb. If either test is positive, such patients should be treated with lamiVUDine during chemotherapy and for six months afterwards. 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: