# BC Cancer Protocol Summary for Treatment of Relapsed/Refractory Mantle-Cell Lymphoma Using iBRUtinib

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| ***Protocol Code*** | *LYMIBRU* |
| ***Tumour Group*** | *Lymphoma* |
| ***Contact Physicians*** | *Dr. Laurie Sehn*<br>*Dr. Alina Gerrie* |

**ELIGIBILITY**:

- Relapsed or refractory mantle-cell lymphoma with at least one prior therapy
- AST or ALT less than 3 x ULN

**TESTS**:

- Baseline (required before first treatment): CBC & Diff, creatinine, total 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, HbsAb, HBcoreAb
- Each time seen by physician: CBC & Diff, total bilirubin, ALT
- If clinically indicated: creatinine, PTT, INR, ECG, MUGA scan or echocardiogram
- If clinically indicated: HBV viral load (see protocol SCHBV)

**CAUTION:**

- Cardiac risk factors including history of hypertension, diabetes mellitus, cardiac arrhythmia, cardiac failure

**PREMEDICATIONS**:

- None

**SUPPORTIVE MEDICATIONS:**

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

**TREATMENT**:

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| iBRUtinib | 560 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 to 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 | Mantle-cell lymphoma iBRUtinib dose modification for myelosuppression after recovery |
|---|---|
| 1st | Restart at 560 mg daily |
| 2nd | Restart at 420 mg daily |
| 3rd | Restart at 280 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 420 mg PO daily |
| | Second occurrence: Hold until improvement to grade 1 or baseline. Restart at 280 mg PO daily |
| | Third occurrence: Discontinue iBRUtinib |
| Grade 3 cardiac arrhythmias | First occurrence: Hold until improvement to grade 1 or baseline. Restart at 420 mg PO daily |
| | Second occurrence: discontinue iBRUtinib |
| Grade 3 or 4 cardiac failure<br>or<br>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 |
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| 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. **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; 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. 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.
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. **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.
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.

**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. Dreyling M, Jurczak W, Jerkeman M. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Lancet 2016;387(10020):770-8.
2. Janssen Inc. IMBRUVICA® product monograph. Toronto, Ontario; 29 June 2022.