Special Considerations for the Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib)
SPECIAL CONSIDERATIONS FOR THE USE OF B-CELL RECEPTOR INHIBITORS (IBRUTINIB AND IDELALISIB) \(^1,2,3\)

**IBRUTINIB**

- **Dosage**
  - CLL: The recommended dose of ibrutinib is 420 mg PO daily, continuous
  - MCL: The recommended dose of ibrutinib is 560 mg PO daily, continuous

- **Lymphocytosis**
  - CLL: Upon initiation of ibrutinib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and may persist for several weeks on treatment.
  - MCL: Upon initiation of ibrutinib, transient increase in absolute lymphocyte counts occurred in 33% of patients. The onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and resolves by a median of 8 weeks.

- Grade \(\geq 2\) bleeding events were observed in 6% of patients on ibrutinib; the mechanism is not well-understood. Consider the benefit-risk of ibrutinib in patients requiring anti-platelet or anticoagulant therapies. Clinical trials excluded subjects on concurrent warfarin.

- New onset atrial fibrillation was reported in <5%, associated with ibrutinib administration.\(^2\)

**Co-administration with CYP3A inhibitors and inducers** \(^2,3\)

- Avoid concomitant administration of ibrutinib/idelalisib with strong or moderate inhibitors of CYP3A.
  - For strong CYP3A inhibitors used short-term (eg, antifungals and antibiotics for 7 days or less; eg, ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting ibrutinib/idelalisib therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically.
  - If a moderate CYP3A inhibitor must be used, reduce the ibrutinib/idelalisib dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of ibrutinib/idelalisib toxicity.

- Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, St. John's Wort). Consider alternative agents with less CYP3A induction.

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1. Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at [www.fda.gov](http://www.fda.gov).

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**IDELALISIB**

- The recommended dose of idelalisib is 150 mg PO twice daily, per prescribing recommendations.

- Fatal and/or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.
  - Hepatotoxicity: Monitor hepatic function prior to and during treatment. Interrupt (if ALT/AST \(> 5\times ULN\) (upper limit of normal) and when resolved may resume at a reduced dose (100 mg PO twice daily).
  - Diarrhea or Colitis: Monitor for the development of severe diarrhea or colitis. Interrupt until resolution and then reduce or discontinue idelalisib. Severe diarrhea and colitis can be managed with systemic or nonabsorbable steroids.
  - Pneumonitis: Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Discontinue idelalisib.
  - Intestinal perforation: Discontinue idelalisib if intestinal perforation is suspected.

- **Lymphocytosis**
  - CLL: Upon initiation of idelalisib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of idelalisib therapy and may persist for several weeks on treatment.