Written By: Kirollos Hanna, PharmD, BCPS, BCOP, FACCC, FAPO
Minnesota Oncology, St. Paul, MN

Positive Quality Intervention: Zanubrutinib (Brukinsa ®) treatment for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Description:

The purpose of this PQI is to discuss clinical considerations around the use of zanubrutinib (Brukinsa®) to optimize outcomes for patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Background:

Zanubrutinib is a potent, highly selective, and irreversible inhibitor of Bruton's tyrosine kinase (BTK) with FDA approval for treatment of CLL/SLL.[1] Efficacy and safety of zanubrutinib in patients with CLL/SLL was shown in two pivotal studies. The phase 3 SEQUOIA trial compared zanubrutinib, given until disease progression or intolerable toxicity, vs bendamustine plus rituximab (BR), given for 6 cycles, in patients with treatment-naive CLL/SLL. Patients were stratified into two cohorts, one without deletion 17p [del(17p)], with these patients undergoing 1:1 randomization to either zanubrutinib or BR, and a second cohort positive for del(17p) who were treated with zanubrutinib monotherapy. At a median follow up of 43.7 months, median progression-free survival (mPFS) in the 479 patients without del(17p) was not estimable in the zanubrutinib group compared to 42.2 months in the BR group (HR 0.30;95% CI 0.21-0.43; $P < 0.0001$). In the 110 patients with del(17p) treated with zanubrutinib monotherapy, PFS and overall survival (OS) of 42 months was seen in 79.4% (95% CI 70.4-85.9) and 89.5% (95% CI 81.9-94.1) of patients, respectively.[2] The phase 3 ALPINE trial was a head-to-head, randomized (1:1) comparison of zanubrutinib vs ibrutinib in 652 patients with relapsed or refractory CLL or SLL who had received at least one previous therapy. At an extended follow-up of 39 months, the PFS rates were 65.8% with zanubrutinib and 54.3% with ibrutinib (HR 0.68; 95% CI 0.53-0.86; $P = 0.0011$). This benefit was sustained across subgroups including patients with del(17p) (HR 0.52; 95% CI 0.33-0.83).[3] In pooled safety analysis from these trials, the most common adverse reactions in zanubrutinib patients (≥30%), including laboratory abnormalities, were neutrophil count decreased (51%), platelet count decreased (41%), upper respiratory tract infection (38%), hemorrhage (32%), and musculoskeletal pain (31%).[1] The selectivity of zanubrutinib for BTK with minimal off-target effects may make it a more tolerable treatment for CLL/SLL patients who are intolerant to other BTK inhibiting agents. Shadman and colleagues studied full dose zanubrutinib tolerability in 82 patients, 61 with CLL/SLL, with previous intolerance to either ibrutinib or acalabrutinib +/- ibrutinib. At a median follow-up of 25.2 months, 67.7% ibrutinib-related and 73.0% acalabrutinib-related intolerance events did not recur. The most common adverse events seen during zanubrutinib treatment were fatigue (29.3%), bruising (22%), arthralgia (20.7%), COVID-19 (20.7%), and diarrhea (20.7%).[4]

PQI Process:

- Upon receipt of an order for Zanubrutinib for CLL/SLL:
  - Verify patient dose to be 160 mg by mouth every 12 hours or 320 mg by mouth once daily with or without food
    - Selection of dosing strategy should take into account pill burden and patient's ability to adhere to therapy.
    - Patient comorbidities may make zanubrutinib a safer option (ex. history of Afib, recent hemorrhage, hypertension, concomitant PPI or H2R antagonists)
- Modify zanubrutinib dose accordingly if co-administered with:
  - Strong CYP3A inhibitor – 80 mg once daily
  - Moderate CYP3A inhibitor – 80 mg twice daily

    - Moderate or Strong CYP3A inducer – avoid concomitant use
    - If a moderate CYP3A inducer cannot be avoided, the dose may be increased to 320 mg twice daily.
    - Reduce dose to 80 mg twice daily in patients with severe hepatic impairment (Child-Pugh Class C)
- Consider prophylaxis for herpes simplex virus, Pneumocystis jirovecii pneumonia, and other infections according to standard of care in patients at increased risk for infections
- If a dose is missed, it should be taken as soon as possible on the same day then return to the normal schedule the following day.
- Verify monitoring parameters:
    - CBC with differential, hepatic function
    - Signs/symptoms of Afib/flutter, bleeding, or infections including opportunistic infections
- Asymptomatic lymphocytosis should not be regarded as an adverse reaction, and these patients should continue taking zanubrutinib[1]
- Consider the benefit-risk of withholding zanubrutinib for 3-7 days before and after surgery depending upon the type of surgery and the risk of bleeding[1]
- See full prescribing information for dose modifications with Grade 3 or worse adverse effects

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) sheet
- Counsel to administer orally, review once a day vs twice a day dosing
- Proper sign/symptom monitoring
- Evaluate if patients have missed any doses between cycles; consider reminders, calendars, pill box, etc
- Patient Assistance:
    - NCODA Financial Assistance Tool
    - myBeiGene Patient Support Program

References:

1. Zanubrutinib PI
2. Munir T, et al. P639: ZANUBRUTINIB (ZANU) VS BENDAMUSTINE + RITUXIMAB (BR) IN PATIENTS (PTS) WITH TREATMENT-NAÏVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL): EXTENDED FOLLOW-UP OF THE SEQUOIA STUDY. Hemasphere. 2023 Aug 8;7(Suppl):e15364af. doi: 10.1097/01.HS9.
3. Brown J, et al. Extended Follow-up of ALPINE Randomized Phase 3 Study Confirms Sustained Superior Progression-free Survival of Zanubrutinib Versus Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL). Presented at: American Society of Hematology Annual Meeting & Exposition; December 7-10, 2023; San Diego, California.
4. Shadman M, et al. P633: UPDATED SAFETY AND EFFICACY RESULTS OF ZANUBRUTINIB IN PATIENTS WITH B-CELL MALIGNANCIES WHO ARE INTOLERANT OF IBRUTINIB AND/OR ACALABRUTINIB. Hemasphere. 2023 Aug 8;7(Suppl):e70152b3. doi: 10.1097/01.HS9.