



Positive Quality Intervention: Acalabrutinib (Calquence®) In Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Description: The purpose of this PQI is to discuss the clinical considerations around the use of acalabrutinib (Calquence®) to optimize the outcomes for patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL).

Background: Acalabrutinib is a Bruton's tyrosine kinase (BTK) inhibitor initially indicated for mantle cell lymphoma (MCL) patients who have received at least one prior therapy. In late 2019, it received an indication for the treatment of CLL/SLL either as monotherapy or in combination with obinutuzumab.¹ Efficacy in the front-line setting was established by the ELEVATE-TN trial, which demonstrated a progression-free survival (PFS) advantage of acalabrutinib when administered with or without obinutuzumab, over obinutuzumab plus chlorambucil.² Additionally, at a median follow up of 28.3 months, acalabrutinib plus obinutuzumab improved PFS and overall response rate (ORR) compared with obinutuzumab plus chlorambucil (ORR 94% vs. 78.5%, PFS 93% vs. 47% respectively).² The ASCEND trial displayed an advantage in PFS of acalabrutinib monotherapy in the relapsed/refractory setting when compared to the investigator's choice of rituximab product plus idelalisib or bendamustine.³ As monotherapy, acalabrutinib significantly improved PFS in both the ELEVATE-TN and in the ASCEND trial, with 24 months and 16.5 months respectively. ORR was not significantly improved in both ELEVATE-TN (86% vs. 78.5%) and ASCEND (79% monotherapy vs. 83% idelalisib plus rituximab (I-R) or bendamustine plus rituximab (B-R)). ASCEND trial PFS: not reached in monotherapy vs. 16.5 months for the I-R/B-R arm.³ In ELEVATE-RR, a trial that puts acalabrutinib head-to-head with ibrutinib as monotherapies, acalabrutinib had a non-inferior PFS compared to ibrutinib. At a median follow up of 41 months, acalabrutinib had a PFS of 38.4 months compared 38.4 months with ibrutinib. In terms of safety outcomes, acalabrutinib had less cardiotoxicity and less discontinuations due to adverse events.⁴ Acalabrutinib, as compared to ibrutinib, displayed less atrial fibrillation (9.4% vs 16.0%), less hypertension (9% vs 23%), and had less discontinuations due to adverse events (15% vs 22%).

PQI Process:

Upon the receipt of a new prescription of acalabrutinib for CLL/SLL:

- Verify dose: acalabrutinib 100 mg by mouth every 12 hours, taken whole with water, with/without food
 - If dose is missed by > 3 hours, skip and take the next at its regularly scheduled time
 - Avoid in severe hepatic impairment
 - No dose adjustment needed in mild to moderate hepatic or renal impairment (use in severe renal impairment or with dialysis has not yet been evaluated)
- Review patient medication list for possible drug-drug interactions
 - Strong CYP3A4 inducer: if use cannot be avoided, increase dosage to 200 mg every 12 hours
 - Strong CYP3A4 inhibitor: avoid use, but if the inhibitor is a short-term medication, stop acalabrutinib and resume after inhibitor is complete
 - Moderate CYP3A4 inhibitor: reduce dosage to 100 mg daily
 - Administration with tablet formulation may be co-administered with gastric reducing agents
- In combination with obinutuzumab, acalabrutinib should be taken **BEFORE** the obinutuzumab

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Adverse Events and Management¹

Category	Occurrence	Action
Fatal/serious infections, including opportunistic infections	Serious or \geq Grade 3 infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients in clinical trials.	Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor for signs and symptoms of infection and treat promptly.
Fatal and serious hemorrhagic events	Major hemorrhage (serious or \geq Grade 3 bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.	Monitor patients for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3-7 days pre- and post-surgery depending on type of surgery and the risk of bleeding. Caution in patients on antithrombotic agents.
Grade 3 or 4 Cytopenias	Neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients. Grade 4 neutropenia developed in 12% of patients.	Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted.
Cardiac Factors	<u>Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients.</u> The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection.	Monitor for symptoms of arrhythmia (ex. palpitations, dizziness, syncope, dyspnea) and manage as appropriate.
Skin Cancer	The most frequent second primary malignancy was skin cancer (6%)	Monitor patients for skin cancer and advise protection from sun exposure.

Dose Modifications¹

Event	Occurrence	Dose Modification (Starting dose = 100 mg every 12 hours)
Grade 3 or greater non-hematologic toxicities	First and Second	Hold acalabrutinib; once toxicity has resolved to Grade 1 or baseline level, acalabrutinib may be resumed at 100 mg approximately every 12 hours
Grade 3 thrombocytopenia with bleeding	Third	Hold acalabrutinib; once resolved to Grade 1 or baseline level, resume at a reduced frequency of 100 mg daily
Grade 4 thrombocytopenia		
Grade 4 neutropenia lasting longer than 7 days	Fourth	Discontinue acalabrutinib

Patient-Centered Activities:

- Patient Education
 - Provide [Oral Chemotherapy Education \(OCE\)](#) sheet and review with patient
 - Instruct patient to report any signs or symptoms of atrial fibrillation or flutter such as palpitations, dizziness, faint, chest discomfort
 - Patient should be made aware of the increased bleeding risk associated with acalabrutinib
 - Due to this risk, they may need to hold their medication prior to any procedures

- Ensure patient has access to supportive medications for diarrhea such as loperamide
- Patient Assistance: [NCODA Financial Assistance Tool](#)

Supplemental Information:

- Acalabrutinib is only available as tablets in the United States
 - Capsules should be avoided with proton pump inhibitors
 - If other gastric acid reducing agents are used, recommend taking acalabrutinib 2 hours prior to taking a H2 receptor antagonist; separate dosing by at least 2 hours if using an antacid

References:

1. [Calquence® \(acalabrutinib\) \[prescribing information\]. Wilmington, DE: AstraZeneca Pharmaceuticals LP.](#)
2. Sharman JP, et al. Acabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naïve chronic lymphocytic leukemia (ELEVATE TN): a randomized, controlled, phase 3 trial. *Lancet*. 2020 Apr 18;395(10232):1278-1291.
3. Ghia P, et al. ASCEND: Phase III, Randomized Trial of Acabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *J Clin Oncol*. 2020 Sept 01;38(25):2849-2861.
4. Byrd J, et al. Acabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. *J Clin Oncol*. 2021 Nov 01;39(31):3441-3452.