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NCCN Guidelines Panel: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for "Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma" for the recategorization of CALQUENCE® (acalabrutinib) for the treatment of adults with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) based on results from the Phase 3 ASCEND (ACE-CL-309) trial. CALQUENCE® is an inhibitor of Bruton tyrosine kinase (BTK).

Specific Changes:

Request moving acalabrutinib to a Preferred regimen and a category revision to category 1 for the treatment of all R/R CLL/SLL patients (including) without del(17p)/TP53 mutation (CSLL-D 2 of 6) and with del(17p)/TP53 mutations (CSLL-D 3 of 6).

FDA Status:

CALQUENCE is not FDA approved for the treatment of CLL/SLL.

Acalabrutinib was approved by the FDA on 10/31/2017 under the brand name CALQUENCE for the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.¹

Please refer to the CALQUENCE [prescribing information](#) for the full FDA-approved indication and safety information.

Rationale: ASCEND is the first randomized, controlled trial in R/R CLL to demonstrate monotherapy superiority against standard of care combinations, including a combination with a novel agent. Background and results from publicly available information are as follows:²

Study Details:

- ASCEND is a randomized, multicenter trial conducted in R/R CLL patients which evaluated the efficacy and safety of acalabrutinib monotherapy versus rituximab + investigator's choice of bendamustine (BR) or ibrutinib (IdR).
- The ACE-CL-309 (ASCEND) study included adults with confirmed CLL (N=310) with ≥1 prior systemic therapy for CLL. Patients were stratified by del(17p), ECOG status, and prior therapies. Eighteen percent had del(17p), 25% had del(11q), 32% had a complex karyotype and 77% of patients had an unmutated immunoglobulin variable region heavy chain (IGHV). The median age was 68 years old and 42% of patients were Rai stage III-IV.²
- At a median follow-up of 16.1 months, the IRC-assessed median PFS was not reached in the acalabrutinib group and was 16.5 months in the IdR/BR group (HR 0.31, 95% CI, 0.20-0.49; p<0.0001). There was 69% reduction in risk of progression or death with acalabrutinib. PFS rates at 12 months were 88% with acalabrutinib and 68% with IdR/BR. Acalabrutinib met its primary endpoint at interim analysis. IRC-assessed ORR was 81% in the acalabrutinib group and 76% in the IdR/BR group (P=0.22).² Overall Survival (OS) rates at 12 months were 94% for acalabrutinib group and 91% for the IdR/BR group.³

- The most common AEs occurring in ≥15% of patients with acalabrutinib were headache (22%), neutropenia (19%), diarrhea (18%), anemia (15%), and cough (15%). Grade ≥3 AEs occurring in ≥5% of patients for the acalabrutinib arm were neutropenia (16%), anemia (12%), and pneumonia (5%). Atrial fibrillation rate was 5% in the acalabrutinib group vs. 3% in the IdR/BR group. Bleeding AEs were 26% on acalabrutinib vs 8% on IdR/BR; including major hemorrhage (2% vs 3%). Secondary primary malignancies excluding NMSC was 6% for acalabrutinib vs 3% for IdR/BR. Eleven percent of patients discontinued due to AE in the acalabrutinib arm vs 49% and 11% in the IdR and BR arms, respectively. The safety profile of acalabrutinib is consistent with previous trials and no new safety signals were found.²

These materials may include information that is not found in the currently approved prescribing information for CALQUENCE. The enclosed information is intended to provide pertinent data and should in no way be construed as a recommendation for the use of this product in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information for CALQUENCE. This information is provided to NCCN evaluators for guideline review purposes only.

Reference(s):

A copy of the approved [Package Insert](#) and publications for acalabrutinib are included for the support of this data.

1. CALQUENCE® (acalabrutinib) Prescribing Information.
2. Ghia P, Pluta A, Wach M, et al. ASCEND Phase 3 study of acalabrutinib vs. investigators' choice of rituximab plus idelalisib (IdR) or bendamustine (BR) in patients with relapsed/refractory chronic lymphocytic leukemia (CLL). Oral presentation at: European Hematology Association 2019 Annual Meeting. Available online. Accessed June 2019.
3. Ghia P, Pluta A, Wach M, et al. ASCEND Phase 3 study of acalabrutinib vs. investigator's choice of rituximab plus idelalisib (IdR) or bendamustine (BR) in patients with relapsed/refractory chronic lymphocytic leukemia (CLL). Abstract LB2606 at: European Hematology Association 2019 Annual Meeting; June 16 2019. Amsterdam, NL.

Sincerely,

Michelle Dawson

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