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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 inclusion of CALQUENCE® (acalabrutinib) for the treatment of adults with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). CALQUENCE® is an inhibitor of Bruton tyrosine kinase (BTK).

Specific Changes:

Request inclusion of acalabrutinib as a treatment option for first-line CLL/SLL, without del(17p)/TP53, therapy in frail patients with significant comorbidities and adults with significant comorbidities (CSLL-D 1 of 5).

Request inclusion of acalabrutinib as a treatment option for first-line CLL/SLL with del(17p)/TP53 mutation (CSLL-D 3 of 5).

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: Results from the Phase 1/2 ACE-CL-001 treatment-naïve cohort support the use of CALQUENCE in this population. Background and results from publicly available information are as follows:

- Acalabrutinib is a selective, small-molecule, irreversible inhibitor of BTK with minimal off-target interactions. In a screen of 395 mammalian wild-type kinases, acalabrutinib IC₅₀ concentrations for ERBB4 and BMX were 3 and 9-fold higher (less potent) than for BTK in biochemical kinase assays. IC₅₀ values for BTK, ERBB4 and BMX are as follows: 5.1 nM, 16 nM, and 46 nM, respectively. IC₅₀ values for other kinases were greater than 100 nM. Acalabrutinib had minimal activity on other immune cells (T cells and NK cells).^{2,3}
- In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and survival.¹
- Acalabrutinib demonstrates rapid oral absorption and a short half-life, allowing for more frequent dosing. An increase in the de novo synthesis rate of BTK has been theorized for B-cell malignancies with more rapidly proliferating cells. Dosing acalabrutinib twice daily achieved a continuous BTK binding of ≥ 95% over a period of 24 hours.^{2,3}

Study Details:⁴

- The ACE-CL-001 treatment-naïve cohort included adults with confirmed CLL (N=99) in whom chemotherapy was contraindicated or was declined by the patient. Sixty-two percent had

unmutated IGHV, 10% had del17p, 15% had TP53 mutation and 20% of patients had a complex karyotype. The median age was 64 years old and 47% of patients were Rai stage III-IV.

- The median time on acalabrutinib was 42 months (range, 1 – 48 months) and 88 patients (89%) remain on acalabrutinib therapy.
- In this trial, the most common AEs ($\geq 20\%$, all grades) were diarrhea (49%), headache (44%), upper respiratory tract infection (40%), contusion (39%), arthralgia (33%), weight increased (31%), nausea (30%) and cough (23%). Grade 3/4 AEs ($\geq 5\%$) were neutropenia (8%), hypertension (7%), diarrhea (5%) and headache (5%). Atrial fibrillation and hypertension (all grades) occurred in 6% and 17% of patients, respectively, with Grade 3 events occurring in 2% and 7% of patients. Bleeding events (all grades) occurred in 64% of patients with contusion being most common (39%). All but three (3% Grade 3) bleeding events were Grade 1/2 events and no patients discontinued due to bleeding. Overall, 11% of patients discontinued treatment, 5% of which were due to AEs, including secondary malignancies (angiosarcoma, glioblastoma multiforme, small cell lung cancer), sepsis (Grade 4) and urinary tract infection (Grade 3). One Grade 5 event (multiorgan failure) in the setting of pneumonia was reported, which was considered unrelated to Calquence.
- Acalabrutinib demonstrated the following clinical activity: Overall response rate (ORR) of 97%, a complete response of 5%, and partial response of 92%. The ORR for each high-risk subgroup [unmutated IGHV, del(17p), TP53 mutation, complex karyotype] was 100%. Median duration of response (DOR) was not reached and the 36-month DOR rate was 98% (95% CI, 90% - 99%). The median progression free survival (PFS) was not reached and the 36-month PFS was 97% (95% CI, 91% - 97%). Median event free survival (EFS) was not reached and the 36-month EFS was 92% (95% CI, 84% - 96%).

An in-depth safety analysis of CALQEUNCE monotherapy was undertaken on a combined safety database of 612 patients with hematological malignancies (CLL, DLBCL, FL, MCL, MM and WM). The results of this analysis formed the basis of the warnings and precautions for CALQUENCE monotherapy and included: hemorrhage, infection, cytopenias, second primary malignancies, and atrial fibrillation and flutter.

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. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): A Covalent Bruton Tyrosine Kinase Inhibitor with a Differentiated Selectivity and In Vivo Potency Profile. *J Pharmacol Exp Ther*. 2017;363(2):240-252.
3. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med*. 2016;374(4):323-332.
4. Byrd J, Woyach J, et al. Acalabrutinib in Treatment-Naïve (TN) Chronic Lymphocytic Leukemia (CLL): Updated Results from the Phase 1/2 ACE-CL-001 Study. Oral presentation at: American Society of Hematology 2018 Annual Meeting; December 2018; San Diego, CA.

Sincerely,

Michelle Dawson

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