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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) in the front-line setting based on the recent peer-reviewed publication of the ELEVATE-TN study (Sharman et al., *Lancet*. 2020; 395: 1278–91). CALQUENCE is an inhibitor of Bruton tyrosine kinase (BTK).

Specific Changes:

Request inclusion of acalabrutinib ± obinutuzumab as a Preferred, Category 1 regimen for first-line CLL/SLL, without del(17P)/TP53 (CSLL-D 1 of 6).

FDA Status:

Acalabrutinib was approved by the FDA on 11/21/2019 under the brand name CALQUENCE for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).²

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

Rationale: ELEVATE-TN is the first randomized trial to study a BTK inhibitor (BTKi) monotherapy and in combination with obinutuzumab vs chemoimmunotherapy in patients with previously-untreated CLL. Both the acalabrutinib combination and monotherapy arms demonstrated a statistically-significant and clinically-meaningful improvement in progression-free survival (PFS) when compared with the chemotherapy-based combination of chlorambucil and obinutuzumab. The safety and tolerability profile of acalabrutinib was consistent with previous trials.

Study Details:

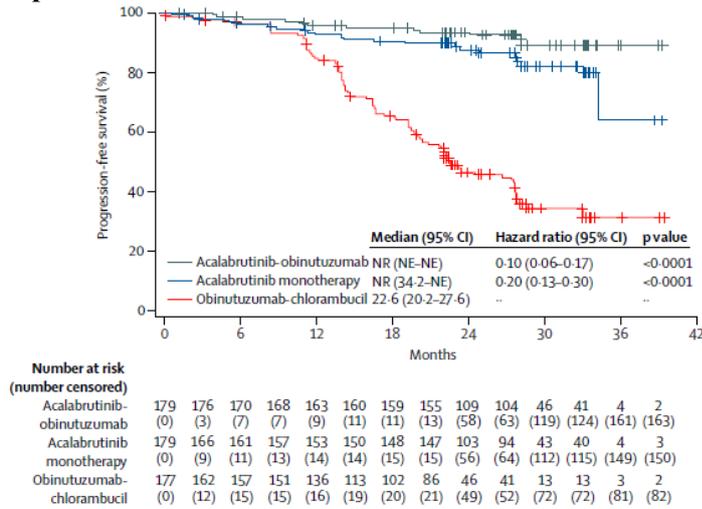
ELEVATE-TN (ACE-CL-007) is a randomized, multicenter, open-label, Phase III trial evaluating the safety and efficacy of acalabrutinib alone or in combination with obinutuzumab vs chlorambucil in combination with obinutuzumab in previously untreated patients with CLL. In the trial, 535 patients were randomized (1:1:1) into three arms. Patients had to be ≥65 years of age, or 18 - 65 years of age with either a total Cumulative Illness Rating Scale (CIRS) > 6 or creatinine clearance of 30 to 69 mL/min were enrolled.

Median age was 70 years (interquartile range [IQR] 66-75), and 448 (84%) of 535 patients were aged 65 years or older. Chronic lymphocytic leukemia international prognostic index score was high risk in 368 (69%), and very high risk in 66 (12%) of 535 patients. Del(17)(p13.1) was present in 49 (9%) patients, del(11)(q22.3) was present in 95 (18%) patients, TP53 mutation was present in 61 (11%) patients, unmutated IGHV was present in 338 (63%) patients, and 92 (17%) patients had complex karyotype (defined as 3 or more cytogenetic abnormalities based on karyotyping by the central laboratory). After a median follow-up of 28.3 months (IQR 25.6-33.1), median PFS (assessed by an Independent Review Committee [IRC]) was significantly longer with acalabrutinib-obinutuzumab (not reached [NR], 95% CI not evaluable [NE]-NE) than with obinutuzumab-chlorambucil (22.6 months, 20.2-27.6), with a 90% reduction in relative risk of progression or death with acalabrutinib-obinutuzumab (HR 0.10, 0.06-0.17; p<0.0001). Median PFS was significantly longer with

acalabrutinib monotherapy (NR, range 34.2-NE) versus obinutuzumab-chlorambucil (22.6, 95% CI 20.2-27.6), with an 80% reduction in relative risk of progression or death with acalabrutinib monotherapy (HR 0.20, 95% CI 0.13-0.30; p<0.0001).

The best overall response was significantly better with acalabrutinib-obinutuzumab (94%, 95% CI 89-97%) versus obinutuzumab-chlorambucil (79%, 72-84%; p<0.0001). Overall response was 86% for acalabrutinib monotherapy (95% CI 80-90%, p=0.08 vs obinutuzumab-chlorambucil). More patients had IRC-assessed complete response (including complete response with incomplete bone marrow recovery) with acalabrutinib-obinutuzumab (24 [13%] of 179 patients) than with obinutuzumab-chlorambucil (8 [5%] of 177 patients).

Kaplan-Meier Curve of IRC-Assessed PFS in Patients with CLL in ELEVATE-TN



The median duration of exposure was 27.7 months in the acalabrutinib-obinutuzumab group (IQR 25.0-32.8), 27.7 months in the acalabrutinib monotherapy group (24.8-33.0), and 5.6 months in the obinutuzumab-chlorambucil group (5.5-5.9). Safety was assessed by reported and observed AEs, laboratory measurements, and clinical evaluation across the treatment-emergent period, which was defined as the date of the first dose until 30 days after the date of the last dose of study drug or the date a patient started a new anticancer therapy for chronic lymphocytic leukemia, whichever was earliest. The most common adverse events in an acalabrutinib-containing regimen (≥20%) of any grade in ELEVATE-TN were headache, diarrhea, neutropenia, fatigue, contusion, arthralgia, cough, upper respiratory tract infection, and nausea. The most common Grade ≥3 adverse events in an acalabrutinib-containing regimen (>5%) included neutropenia, thrombocytopenia, anemia, and pneumonia. Serious adverse events were reported in 38.8% of patients in the acalabrutinib-obinutuzumab group and 31.8% of patients in the acalabrutinib monotherapy group.

Events of clinical interest included cardiac events (atrial fibrillation, ventricular tachyarrhythmias), bleeding, hypertension, infections, and tumor lysis syndrome, summarized in the table below.

Events—No. (%)	Acalabrutinib-Obinutuzumab (n=178)		Acalabrutinib (n=179)		Obinutuzumab-Chlorambucil (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	25 (14.0)	8 (4.5)	25 (14.0)	9 (5.0)	13 (7.7)	3 (1.8)
Atrial fibrillation	6 (3.4)	1 (0.6)	7 (3.9)	0	1 (0.6)	0
Ventricular tachyarrhythmias	0	0	0	0	0	0
Bleeding	76 (42.7)	3 (1.7)	70 (39.1)	3 (1.7)	20 (11.8)	0
Hypertension	123 (69.1)	37 (20.8)	117 (65.4)	25 (14.0)	74 (43.8)	14 (8.3)
Tumor lysis syndrome	3 (1.7)	2 (1.1)	0	0	15 (8.9)	13 (7.7)

Second primary malignancies were observed in 19 (11%) patients in the acalabrutinib-obinutuzumab group, 16 (9%) patients in the acalabrutinib monotherapy group, and 13 (8%) patients in the chlorambucil-obinutuzumab group. Across all groups, 22 (55%) of the 40 second primary malignancies were nonmelanoma skin cancers.

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. Sharman JP, Egyed M, Jurczak W et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naïve chronic lymphocytic leukemia (ELEVATE TN): a randomized, controlled phase 3 trial. *Lancet*. 2020; 395: 1278–91.
2. CALQUENCE® (acalabrutinib) Prescribing Information.

Sincerely,

Michelle Dawson

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