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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 ELEVATE-TN, as well as previously submitted data from ACE-CL-003 (ASCO 2019), and ACE-CL-001 (ASH 2018). 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).

Request inclusion of acalabrutinib ± obinutuzumab as a Preferred regimen for first-line CLL/SLL with del(17p)/TP53 mutation (CSLL-D 3 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).[1]

Please refer to the CALQUENCE prescribing information for the full FDA-approved indication and safety information.

The FDA approval is based on results from two Phase III trials: ELEVATE-TN (ACE-CL-007) and ASCEND (ACE-CL-309).

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 chronic lymphocytic leukemia (CLL). Both the acalabrutinib combination with obinutuzumab 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 CALQUENCE 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.

The overall median age was 70 years (range: 41 to 91 years), 47% had Rai stage III or IV disease, 14% had 17p deletion or TP53 mutation, 63% of patients had an unmutated IGVH, and 18% had 11q deletion. Baseline demographic and disease characteristics were similar between treatment arms. Efficacy was based on progression-free survival (PFS) as assessed by an Independent Review

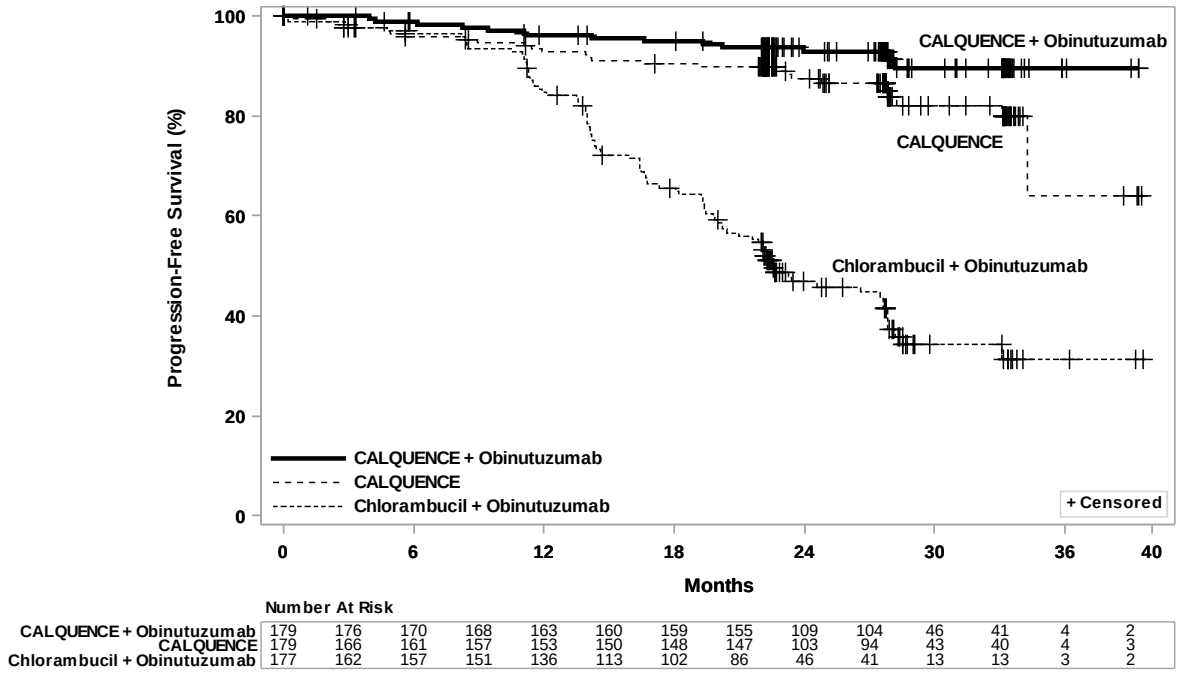
Committee (IRC). The median duration of follow-up was 28.3 months (range: 0.0 to 40.8 months). Efficacy results for PFS and overall response rate are presented in the table below. The Kaplan-Meier curves for PFS are shown in Figure 1.

Table 1. Efficacy Results per IRC in Patients with CLL -- ITT population (ELEVATE-TN)	**CALQUENCE plus Obinutuzumab N=179**	**CALQUENCE Monotherapy N=179**	**Obinutuzumab plus Chlorambucil N=177**
Progression-Free Survival [a]			
Number of events (%)	14 (8)	26 (15)	93 (53)
PD, n (%)	9 (5)	20 (11)	82 (46)
Death events, n (%)	5 (3)	6 (3)	11 (6)
Median (95% CI), months [b]	NE	NE (34, NE)	22.6 (20, 28)
HR[c] (95% CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-
p-value [d]	< 0.0001	< 0.0001	-
Overall Response Rate[a] (CR + CRi + nPR + PR)			
ORR, n (%)	168 (94)	153 (86)	139 (79)
(95% CI)	(89, 97)	(80, 90)	(72, 84)
p-value [e]	< 0.0001	0.0763	-
CR, n (%)	23 (13)	1 (1)	8 (5)
CRi, n (%)	1 (1)	0	0
nPR, n (%)	1 (1)	2 (1)	3 (2)
PR, n (%)	143 (80)	150 (84)	128 (72)

ITT=intent-to-treat; CI=confidence interval; HR=hazard ratio; PD=progressive disease; NE=not estimable; CR=complete response; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response.

[a] Per 2008 International Workshop on CLL (IWCLL) criteria, [b] Kaplan-Meier estimate, [c] Based on a stratified Cox-Proportional-Hazards model. Both hazard ratios are compared with the obinutuzumab and chlorambucil arm, [d] Based on a stratified log-rank test, with an alpha level of 0.012 derived from alpha spending function by the O'Brien-Fleming method, [e] Based on a stratified Cochran–Mantel–Haenszel test, for the comparison with the obinutuzumab and chlorambucil arm.

Figure 1: Kaplan-Meier Curve of IRC-Assessed PFS in Patients with CLL in ELEVATE-TN



The median duration of exposure to CALQUENCE in the CALQUENCE+G and CALQUENCE monotherapy arms was 27.7 months and in the obinutuzumab and chlorambucil arm the median number of cycles was 6. As such the reporting period for adverse reactions (date of the first dose of study drug through 30 days after the date of the last dose of study drug or the first date starting new anticancer therapy for CLL) was shorter in the obinutuzumab + chlorambucil arm than the CALQUENCE containing arms. Serious adverse reactions were reported in 39% of patients in the CALQUENCE + obinutuzumab arm and 32% in the CALQUENCE monotherapy arm, most often due to events of pneumonia (2.8% to 7%). The most common adverse reactions in an acalabrutinib containing regimen (≥20%) of any grade in ELEVATE-TN trial were infection, neutropenia*, anemia*, thrombocytopenia*, headache, diarrhea, upper respiratory tract infection, musculoskeletal pain, fatigue, bruising, lower respiratory tract infection, rash, arthralgia, dizziness, nausea and hemorrhage. The most common (>5%) Grade ≥ 3 adverse reactions were neutropenia*, infection, anemia*, thrombocytopenia*, lymphocytosis, and lower respiratory tract infection. Other clinically relevant adverse reactions in recipients of CALQUENCE (monotherapy and combination) include second primary malignancies (10%), including non-melanoma skin cancer (5%), atrial fibrillation or flutter (3.6%), hypertension (5%), and herpesvirus infection (6%).

*Treatment-emergent decreases (all grades) of hemoglobin, platelets, and neutrophils were based on laboratory measurements and adverse reactions.

Additional details on the ELEVATE-TN trial will be presented at the American Society of Hematology Annual Meeting on December 7th, 2019 and the abstract can be found on their website.

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.

Sincerely,

Michelle Dawson

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