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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 long-term follow-up data from two studies - 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 treatment option for first-line CLL/SLL, without del(17P)/TP53 in frail patients with significant comorbidity or adults with significant comorbidities (CSLL-D 1 of 6).

Request inclusion of acalabrutinib ± obinutuzumab as a treatment option for first-line CLL/SLL with del(17p)/TP53 mutation (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: Updated results from the Phase 1/2 ACE-CL-001 treatment-naive cohort (median 42-month follow-up) support the use of CALQUENCE in this population. Background and results from publicly available information are as follows:

Study Details:[2]

- The ACE-CL-001 treatment-naive 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.

- 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 [unmated 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% - 99%). Median event free survival (EFS) was not reached and the 36-month EFS was 92% (95% CI, 84% - 96%).

- In this trial, the most common AEs (≥ 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 (≥ 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.

Rationale: Updated results from ACE-CL-003 treatment-naive (TN) cohort (median 39-month follow-up) support the use of acalabrutinib + obinutuzumab in this population. Background and results from publicly available information are as follows:

Study Detail:[3]

- ACE-CL-003 was a Phase 1b/2 study evaluated the activity and tolerability of acalabrutinib in combination with the CD20 antibody obinutuzumab in TN and R/R CLL.

- The ACE-CL-003 treatment-naive cohort included adults with confirmed CLL (n=19) in untreated patients aged ≥65 years or <65 years and chemoimmunotherapy ineligible. Fifty-three percent had unmutated IGHV, 22% had del17p, 28% had del(11q) mutation and 42% of patients had a complex karyotype. The median age was 61 years old and 53% of patients were Rai stage III-IV.

- The median follow-up in the treatment naïve cohort was 39.4 months (range, 1 – 44.9 months) and 17 patients (90%) remain on acalabrutinib therapy.

- Consistent with earlier follow-up, acalabrutinib demonstrated the following clinical activity: Overall response rate (ORR) of 95%, a complete response of 31.6%, and partial response of 63.2%. Median duration of response (DOR) was not reached and the 39-month DOR rate was 94.4% (95% CI, 66.6% - 99.2%). Higher MRD-negativity rates were observed in the bone marrow of TN (26%) vs R/R (15%) patients. The median progression free survival (PFS) was not reached in either cohort and the 39-month PFS was 94.4% (95% CI, 66.6% - 99.2%) in the TN cohort.

- In this trial, the most common AEs (≥ 35%, all grades) were upper respiratory tract infection (73%), weight increased (72%), maculopapular rash (66%), cough (64%), diarrhea (64%), headache (56%), nausea (54%), arthralgia (46%), dizziness (46%), constipation (45%), contusion (42%), fall (42%), infusion-related reaction (42%), sinusitis (42%), vomiting (42%), hypertension (41%), fatigue (40%), skin lesion (40%), myalgia (37%), peripheral edema (37%), and decreased appetite (36%). Grade ≥3 AEs (≥ 5%) were neutropenia (24%), syncope (11%), platelet count decreased (9%), cellulitis (9%), weight increased (9%), hypertension (7%) and hypophosphatemia (7%). No atrial fibrillation events occurred in the TN cohort during this long-term follow-up period (3.5 years). Bleeding events (any grade) occurred in 71% of patients with contusion being most common (42%). Two R/R patients (4%) had Grade 3 bleeding events, other events were Grade 1/2 with no patients discontinued due to bleeding.

For additional context:
On June 6, 2019, AstraZeneca announced positive results for the Phase III ELEVATE-TN trial of Calquence in patients with previously-untreated chronic lymphocytic leukemia (CLL). Both the Calquence 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.

ELEVATE-TN 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 in the first arm received chlorambucil in combination with obinutuzumab. Patients in the second arm received Calquence (100mg twice daily until disease progression) in combination with obinutuzumab. Patients in the third arm received Calquence monotherapy (100mg twice daily until disease progression).[4]

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. 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.
3. Woyach J, Rogers K, Bhat S, et al. Acalabrutinib With Obinutuzumab in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia: 3-Year Follow-up. Abstract Presented at American Society of Clinical Oncology (ASCO) Annual Meeting; June 3, 2019. Chicago, IL.
4. AstraZeneca Pharmaceuticals LP. Calquence Phase III ELEVATE-TN trial met primary endpoint at interim analysis in previously-untreated chronic lymphocytic leukaemia [press release]. https://www.astrazeneca.com/media-centre/press-releases/2019/calquence-phase-iii-elevate-tn-trial-met-primary-endpoint-at-interim-analysis-in-previously-untreated-chronic-lymphocytic-leukaemia06062019.html. Published June 6, 2019. Accessed July 3, 2019.

Sincerely,

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