Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

July 2022 Volume 20, Issue 7, Supplement 15

***A SPECIAL MEETING REVIEW EDITION***

# Highlights in Chronic Lymphocytic Leukemia From the 2022 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the ASCO Meeting • June 3-7, 2022 • Chicago, Illinois

**Special Reporting on:**

- Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: Five-Year Follow-Up of ELEVATE-TN
- Influence of Racial and Ethnic Identity on Overall Survival in Patients With Chronic Lymphocytic Leukemia
- Acalabrutinib vs Rituximab Plus Idelalisib or Bendamustine in Relapsed/Refractory Chronic Lymphocytic Leukemia: ASCEND Results at ~4 Years of Follow-Up
- Fixed-Duration Ibrutinib + Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Three-Year Follow-Up From the Fixed-Duration Cohort of the Phase 2 CAPTIVATE Study
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**PLUS Meeting Abstract Summaries**

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# Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: Five-Year Follow-Up of ELEVATE-TN

Bruton's tyrosine kinase (BTK) is an essential component of B-cell receptor signaling. Many small-molecule BTK inhibitors have been developed, and BTK inhibition is now a standard of care for the treatment of patients with chronic lymphocytic leukemia (CLL).[1] Acalabrutinib is a next-generation, highly selective BTK inhibitor that is approved by the US Food and Drug Administration (FDA) for the treatment of patients with CLL/small lymphocytic lymphoma (SLL) or with previously treated mantle cell lymphoma (MCL). The approval of acalabrutinib in patients with previously untreated CLL was based on results from the randomized phase 3 ELEVATE-TN trial, which enrolled patients ages 65 years or older (or ages 18-65 years with comorbidities) without significant cardiovascular disease. A total of 535 patients were randomly assigned to acalabrutinib plus obinutuzumab (n=179), single-agent acalabrutinib (n=179), or obinutuzumab plus chlorambucil (n=177). The median age of enrolled patients was 70 years. Deletion 17p (del[17p]) and/or *TP53* mutations were found in 14%.

The improvements seen with acalabrutinib in the original report were maintained at a 4-year analysis.[2,3] After a median follow-up of 46.9 months, the median progression-free survival (PFS) as assessed by the investigators was not reached in both acalabrutinib arms vs 27.8 months with obinutuzumab plus chlorambucil (*P*<.0001).[2,3]

At the 2022 American Society of Clinical Oncology (ASCO) annual meeting, Jeff Sharman, MD, presented results from a 5-year follow-up analysis of the ELEVATE-TN study.[4] The median follow-up was 58.2 months (range, 0-72.0 months). The rates of treatment discontinuation were 35.2% for acalabrutinib plus obinutuzumab and 40.2% for acalabrutinib alone. Adverse events (AEs) were the most common reason for treatment discontinuation. AEs led to discontinuation in 17.3% of patients receiving acalabrutinib plus obinutuzumab and in 15.6% of those receiving acalabrutinib. Among patients in the control arm, 72 (41%) crossed over to the single-agent acalabrutinib arm.

The previously reported PFS benefit reported with acalabrutinib-based therapy was maintained after approximately 5 years. The median PFS was not reached in either acalabrutinib-containing arm vs 27.8 months in the obinutuzumab-plus-chlorambucil arm (hazard ratio [HR] for acalabrutinib plus obinutuzumab vs obinutuzumab plus chlorambucil, 0.11; 95% CI, 0.07-0.16; HR for acalabrutinib vs obinutuzumab plus chlorambucil, 0.21; 95% CI, 0.15-0.30; Figure 1). The estimated 5-year PFS rates were 84% with acalabrutinib plus obinutuzumab and 72% with acalabrutinib monotherapy. Among patients with del(17p) and/or *TP53* mutations, the median PFS was not reached in either acalabrutinib-containing arm vs 17.5

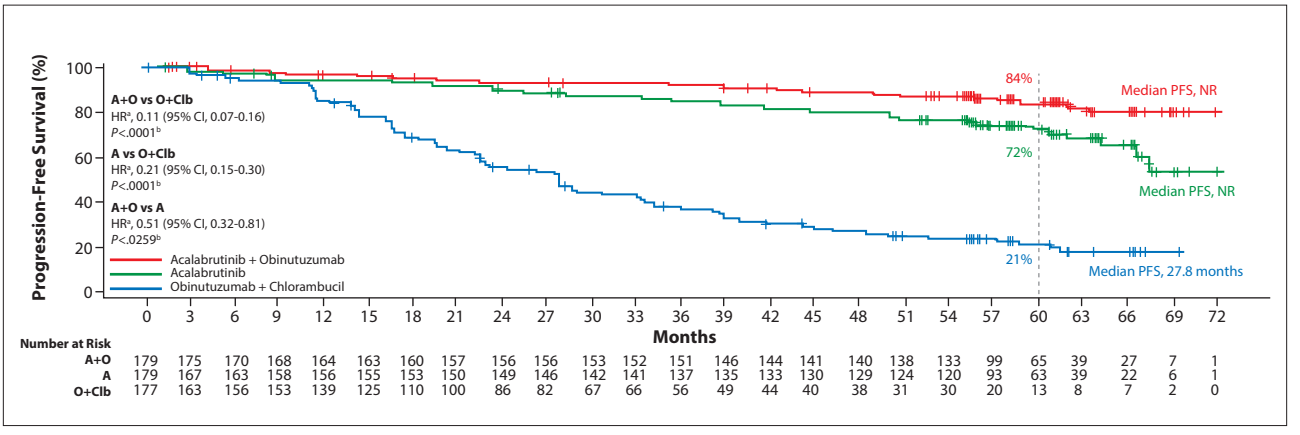


**Figure 1.** Progression-free survival, as assessed by the investigators, in a 5-year follow-up analysis of the phase 3 ELEVATE-TN trial, which compared acalabrutinib monotherapy and acalabrutinib plus obinutuzumab vs obinutuzumab plus chlorambucil in patients with treatment-naive chronic lymphocytic leukemia. [a]The hazard ratio is based on a Cox proportional hazard model stratified by 17p deletion status (yes vs no based on an interactive voice/web response system). [b]The *P* value is based on a log-rank test using the same stratification. A, acalabrutinib monotherapy; A+O, acalabrutinib plus obinutuzumab; HR, hazard ratio; NR, not reached; O+Clb, obinutuzumab plus chlorambucil; PFS, progression-free survival. Adapted from Sharman JP et al. ASCO abstract 7539. *J Clin Oncol.* 2022;40(16 suppl).[4]

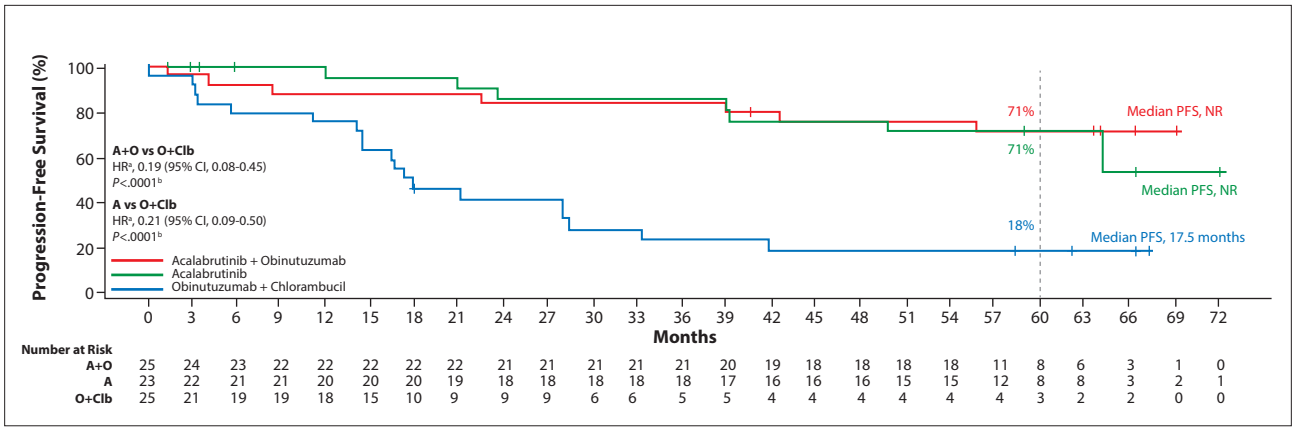


**Figure 2.** Progression-free survival, as assessed by the investigators, among patients with deletion 17p and/or mutated *TP53* in a 5-year follow-up analysis of the phase 3 ELEVATE-TN trial, which compared acalabrutinib monotherapy and acalabrutinib plus obinutuzumab vs obinutuzumab plus chlorambucil in patients with treatment-naive chronic lymphocytic leukemia. [a]The hazard ratio is based on an unstratified Cox proportional hazards model. [b]The *P* value is based on an unstratified log-rank test. A, acalabrutinib monotherapy; A+O, acalabrutinib plus obinutuzumab; HR, hazard ratio; NR, not reached; O+Clb, obinutuzumab plus chlorambucil; PFS, progression-free survival. Adapted from Sharman JP et al. ASCO abstract 7539. *J Clin Oncol.* 2022;40(16 suppl).[4]

months with obinutuzumab plus chlorambucil (HR for acalabrutinib plus obinutuzumab vs obinutuzumab plus chlorambucil, 0.19; 95% CI, 0.08-0.45; HR for acalabrutinib vs obinutuzumab plus chlorambucil, 0.21; 95% CI, 0.09-0.50; Figure 2).

At this analysis, the median overall survival (OS) had not been reached in any arm. However, there was an improvement in OS with acalabrutinib plus obinutuzumab vs obinutuzumab plus chlorambucil (HR, 0.55; 95% CI, 0.30-0.99; *P*=.0474). Response rates were higher in the acalabrutinib-containing arms, with an overall response rate (ORR) of 96.1% with acalabrutinib plus obinutuzumab, 89.9% with acalabrutinib alone, and 83.1% with obinutuzumab plus chlorambucil. The rates of complete response (CR) or CR with incomplete count recovery (CRi) have continued to increase with additional follow-up, reaching 32.4% with acalabrutinib plus obinutuzumab vs 14.5% with acalabrutinib alone at the current analysis. Among patients with a CR/CRi, rates of undetectable minimal residual disease were higher with acalabrutinib plus obinutuzumab (42%) compared with single-agent acalabrutinib (10%) or obinutuzumab plus chlorambucil (9%).

Safety findings were similar to previous analyses. AEs that occurred more frequently in the acalabrutinib-containing arms included headache, diarrhea, and arthralgia. AEs that were more frequent with obinutuzumab plus chlorambucil included neutropenia, nausea, and infusion-related reactions. Cardiac events occurred in 24.2% of patients receiving acalabrutinib plus obinutuzumab, 21.8% of patients receiving acalabrutinib, and 7.7% of patients receiving obinutuzumab plus chlorambucil. Atrial fibrillation occurred in 6.2%, 7.3%, and 0.6% of patients, respectively. Major bleeding occurred in 6.7%, 4.5%, and 1.2% of patients. Hypertension was reported in 9.6%, 8.9%, and 3.6%. Grade 3 or higher infections were more common with acalabrutinib

**ABSTRACT SUMMARY Characteristics and Clinical Outcomes Among Patients Receiving Either Ibrutinib or Anti-CD20 Monotherapy as First-Line Treatment for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: A Retrospective Analysis in Community Oncology Practice**

A retrospective analysis compared outcomes with ibrutinib or anti-CD20 monotherapy as first-line treatment in patients with CLL/SLL receiving care in a community practice between March 2016 and August 2021 (Abstract e19056). Data were available for 3226 patients, of whom 68% received ibrutinib and 32% received an anti-CD20 antibody (rituximab or obinutuzumab). The average age was 71.4 years for patients treated with ibrutinib and 72.9 years for patients treated with an anti-CD20 antibody. Patients receiving ibrutinib were more likely than those receiving an anti-CD20 antibody to have high-risk cytogenetic markers (42.6% vs 27.9%). In an analysis adjusted for baseline differences between groups, ibrutinib was associated with a significantly lower risk of initiating subsequent treatment compared with anti-CD20 antibodies in the overall population (HR, 0.30; *P*<.001), the high-risk cytogenetic subgroup (HR, 0.26; *P*<.001), and patients without results from *IGHV* testing (HR, 0.30; *P*<.001).

plus obinutuzumab (28%) than with acalabrutinib alone (20%). The investigators concluded that acalabrutinib administered as a single agent or as a component of combination therapy is associated with durable disease control and tolerability.

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# Influence of Racial and Ethnic Identity on Overall Survival in Patients With Chronic Lymphocytic Leukemia

The incidence of CLL varies substantially by race and ethnicity, with White individuals accounting for most CLL diagnoses in the United States. According to publicly available data from the Surveillance, Epidemiology, and End Results program, the incidence of CLL is 4.7 per 100,000 White Americans, 3.2 per 100,000 Black Americans, 2.1 per 100,000 Hispanic Americans, and 1.1 per 100,000 Asian Americans.[1] Data for CLL characteristics and outcomes according to race and/or ethnicity are limited. Previous studies indicate that outcomes are worse among CLL patients who are not White. In a 2011 study, OS outcomes were significantly worse in Black patients (n=2059) compared with White patients (n=27,703).[2] The 5-year OS was 63.9% vs 77.1%, respectively (*P*<.01). In a 2013 publication, Black patients with CLL receiving care at 2 institutions (n=84) had higher rates of disease-related complications at diagnosis and higher-risk molecular features compared with a reference non-Black population of 1571 patients.[3] Event-free survival and OS were both significantly shorter in Black patients vs non-Black patients (*P*=.007 and *P*=.0001, respectively).[3] More recently, an analysis of data from the Connect CLL registry showed that OS was shorter among 98 non-White patients vs 1333 White patients (HR, 1.34; *P*=.0445).[4]

To obtain additional knowledge about CLL demographics, treatment, and outcomes based on race/ethnicity, Victoria Vardell, MD, and colleagues analyzed the National Cancer Database

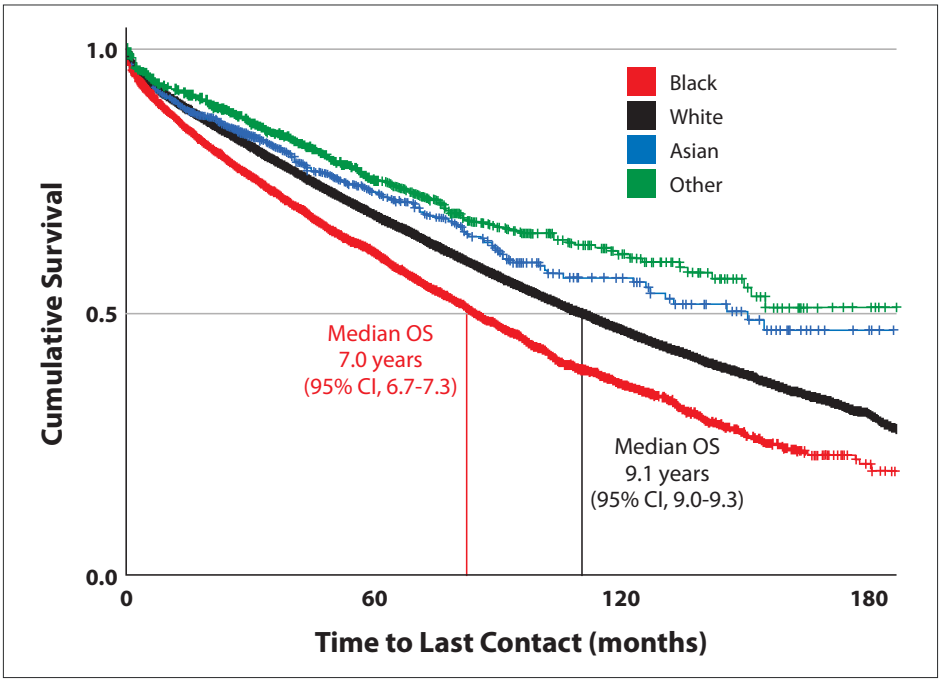


**Figure 3.** Survival according to race/ethnicity in an analysis of the National Cancer Database for Chronic Lymphocytic Leukemia. OS, overall survival. Adapted from Vardell VA et al. ASCO abstract 7508. *J Clin Oncol.* 2022;40(16 suppl).[1]

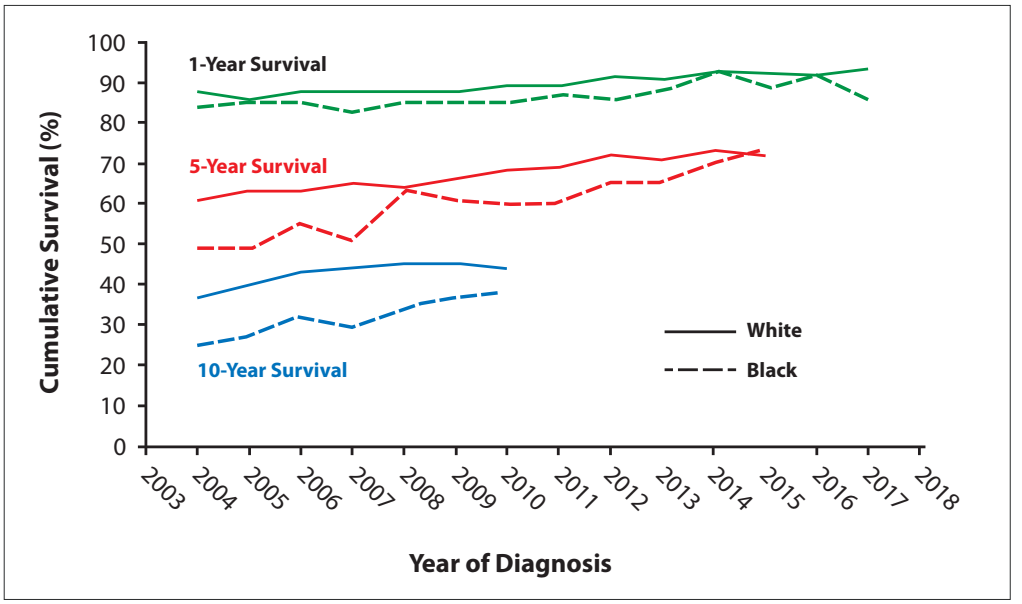


**Figure 4.** Survival over time according to race/ethnicity in an analysis of the National Cancer Database for Chronic Lymphocytic Leukemia. OS, overall survival. Adapted from Vardell VA et al. ASCO abstract 7508. *J Clin Oncol.* 2022;40(16 suppl).[1]

for Chronic Lymphocytic Leukemia, which includes approximately 70% of patients with CLL in the United States.[1] The analysis focused on 97,804 evaluable patients diagnosed between 2004 and 2018 who had racial/ethnic data available. Approximately 91% of patients identified as White, 8% as Black, 3% as Hispanic, 1% as Asian, and 1% as another race. The median age at diagnosis was lower for Black and other racial minority patients (66 years) compared with White patients (70 years). Comorbidity burden as assessed by the Charlson-Deyo Comorbidity Index was also significantly higher among Black patients compared with White patients (0.43 vs 0.31 points).

Compared with White patients, Black patients were more likely to be female (42.8% vs 39.3%), uninsured (6.6% vs 2.1%), or Medicaid-insured (9.9% vs 3.4%), and to reside in low-income areas (47.7% vs 13.1%) or areas with a low high-school graduation rate (41.3% vs 14.3%). Black patients were more likely than White patients to receive systemic CLL-directed therapy at diagnosis (35.9% vs 23.6%). In a multivariate analysis adjusted for age and comorbidity score, the risk of death was significantly higher in Black patients than White patients, with a median OS of 7.0 years and 9.1 years, respectively (HR, 1.51; 95% CI, 1.46-1.57; $P<.001$; Figure 3). Survival over time is shown in Figure 4.

The investigators noted several limitations to the analysis. The racial/ethnic categories may not reflect the complexity of the racial/ethnic background of all patients. In addition, the database does not include staging and molecular risk information, has limited treatment data, and lacks information about the cause of death. However, this analysis—the largest of its kind to date—provides insights into disparities among patients with CLL based on race/ethnicity. CLL appeared to present at a younger age in Black and other racial minority patients compared with White patients. Black patients had significantly more comorbidities and often had increased socioeconomic disadvantages. They were also more likely to receive treatment at diagnosis, which may reflect more advanced disease.

In the era of targeted therapies, OS was significantly shorter in Black patients compared with White patients and those of other races. This discrepancy persisted even after the study investigators adjusted for the patient's age and comorbidity score. The disparity in OS has appeared to improve in the past 15 years. The investigators concluded that the findings should lay the groundwork for strategies to reduce these differences in outcomes. Possible approaches include targeted education to improve early detection and management, as well as additional research to understand disease characteristics and disparities in access to treatment. There is also a need for broader action to address racism, reduce disparities, and build trust between minority patients and the medical community.

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# Acalabrutinib vs Rituximab Plus Idelalisib or Bendamustine in Relapsed/Refractory Chronic Lymphocytic Leukemia: ASCEND Results at ~4 Years of Follow-Up

The FDA approval of acalabrutinib in patients with relapsed/refractory CLL was based on its demonstrated efficacy and safety in the randomized phase 3 ASCEND trial, which compared acalabrutinib vs the investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in patients with relapsed/refractory CLL. The trial enrolled 310 patients, whose median age was 67 years (range, 32-90). The patients had received a median of 2 prior therapies (range, 1-10). The patients were randomly assigned to acalabrutinib or the investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab. Crossover from the control arm to acalabrutinib was allowed after confirmed disease progression.

In the primary analysis of the ASCEND trial, after a median follow-up of 16.1 months, treatment with acalabrutinib led to a significant 69% decrease in the risk of disease progression or death compared with idelalisib plus rituximab or bendamustine plus rituximab.[1] The median PFS was not reached with acalabrutinib vs 16.5 months in the control arm (HR, 0.31; 95% CI, 0.20-0.49; *P*<.001). Acalabrutinib was also associated with an acceptable safety profile. Serious AEs occurred in 29% of patients treated with acalabrutinib, 56% of patients treated with idelalisib plus rituximab, and 26% of patients treated with bendamustine plus rituximab.

After a median follow-up duration of approximately 3 years, the PFS advantage reported with acalabrutinib compared with idelalisib plus rituximab or bendamustine plus rituximab was maintained (HR, 0.29; 95% CI, 0.21-0.41; *P*<.0001).[2] At that time, the median OS was not reached in either arm. No new safety signals were reported.

At the 2022 ASCO meeting, Wojciech Jurczak, MD, presented the final analysis of the study.[3] After a median follow-up of approximately 4 years, the median PFS was still not reached among patients treated with acalabrutinib vs 16.8 months in those treated with idelalisib plus rituximab or bendamustine plus rituximab (HR,

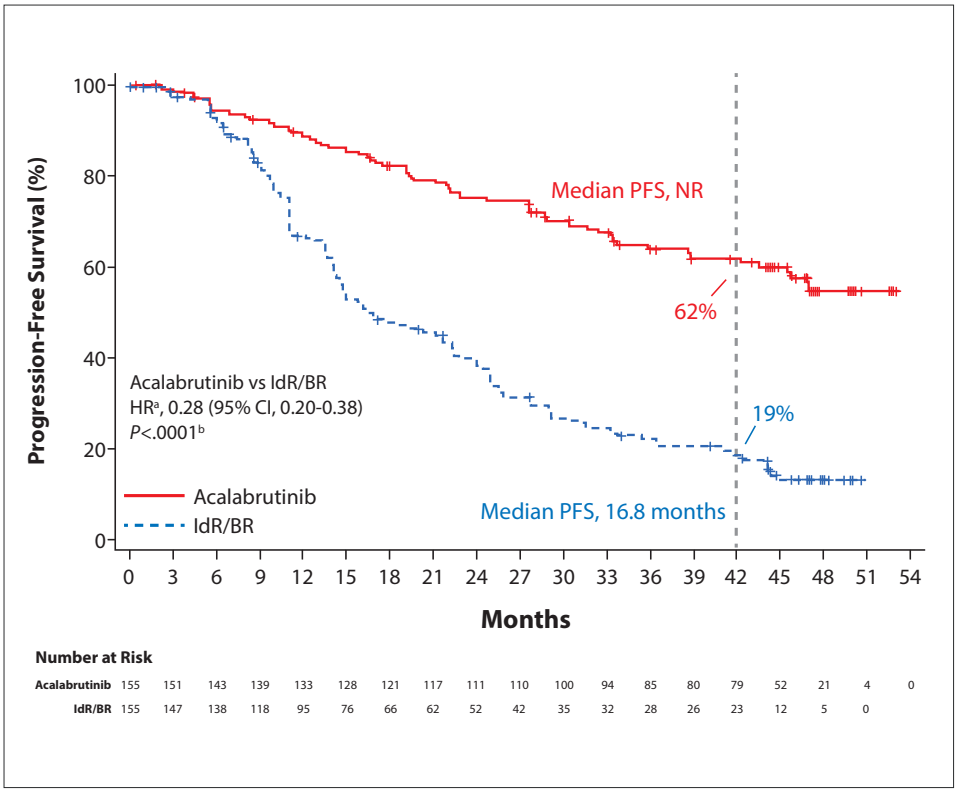


**Figure 5.** Progression-free survival in a 4-year analysis of the phase 3 ASCEND trial, which compared acalabrutinib vs rituximab plus idelalisib or bendamustine in patients with relapsed/refractory chronic lymphocytic leukemia. Because there were no IdR/BR-treated patients at risk by 42 months in the deletion 17p subgroup, 42-month PFS rates were not available for this analysis. [a]The hazard ratio is based on a Cox proportional hazard model, stratified by randomization factors as recorded in an interactive voice/web response system). [b]The *P* value is based on a log-rank test using the same stratification. BR, bendamustine plus rituximab; HR, hazard ratio; IdR, idelalisib plus bendamustine; NR, not reached; PFS, progression-free survival. Adapted from Jurczak W et al. ASCO abstract 7538. *J Clin Oncol.* 2022;40(16 suppl).[3]

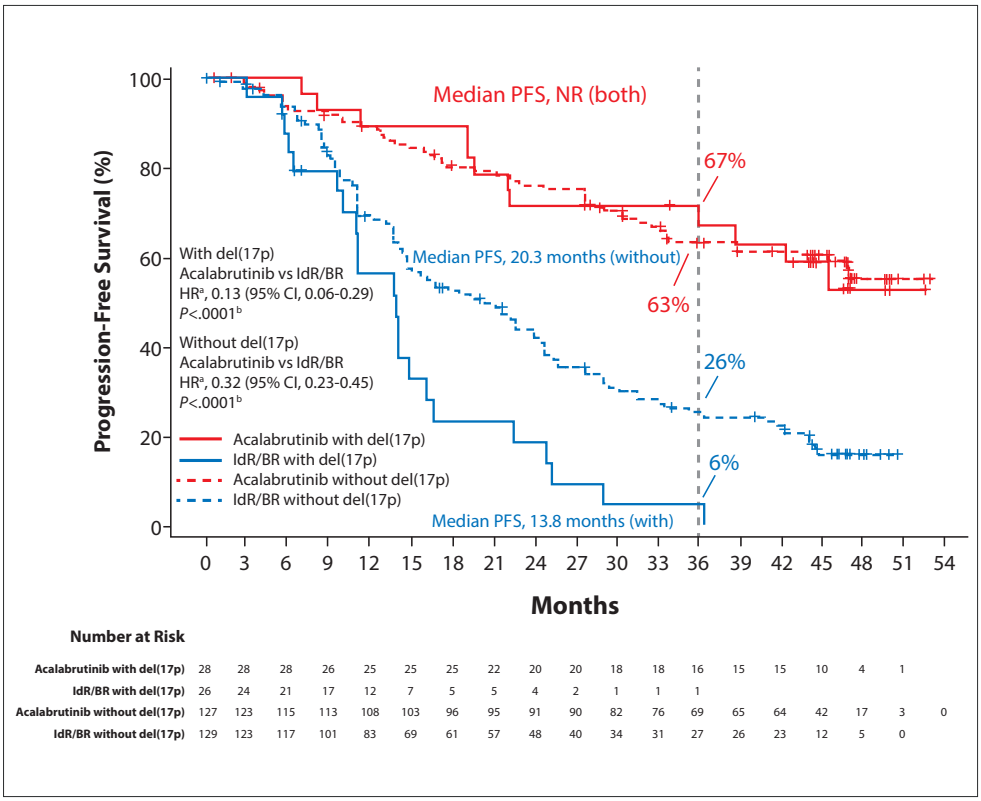


**Figure 6.** Progression-free survival according to del(17p) status in a 4-year analysis of the phase 3 ASCEND trial, which compared acalabrutinib vs rituximab plus idelalisib or bendamustine in patients with relapsed/refractory chronic lymphocytic leukemia. Because there were no IdR/BR-treated patients at risk by 42 months in the deletion 17p subgroup, 42-month PFS rates were not available for this analysis. [a]The hazard ratio is based on an unstratified Cox proportional hazards model. [b]The *P* value is based on an unstratified log-rank test. BR, bendamustine plus rituximab; del(17p), deletion 17p; HR, hazard ratio; IdR, idelalisib plus bendamustine; NR, not reached; PFS, progression-free survival. Adapted from Jurczak W et al. ASCO abstract 7538. *J Clin Oncol.* 2022;40(16 suppl).[3]

0.28; 95% CI, 0.20-0.38; *P*<.0001). The estimated 42-month PFS rates were 62% vs 19%, respectively (Figure 5). Among patients with del(17p), the median PFS was not reached in the acalabrutinib arm vs 13.8 months in the control arm (HR, 0.13; 95% CI, 0.06-0.29; *P*<.0001; Figure 6). The PFS benefit of acalabrutinib was also maintained in patients with the unmutated immunoglobulin heavy-chain variable region (IGHV) gene (HR, 0.20; *P*<.0001) and other subgroups. In the overall population, the median OS was not reached in either arm. The 42-month OS rates were 78% with acalabrutinib vs 65% in the control arm.

In this follow-up analysis, the rates of AEs and events of clinical interest were similar to those reported in the primary analysis. The rates of grade 3 or higher AEs, serious AEs, and AEs leading to dose adjustment or treatment discontinuation were lower with acalabrutinib and bendamustine plus rituximab compared with idelalisib plus rituximab. The most frequent any-grade AEs reported with acalabrutinib were neutropenia, headache, diarrhea, and upper respiratory tract infection. The most common grade 3 or higher AEs were neutropenia, anemia, and pneumonia. Serious AEs reported in at least 5% of patients in any group consisted of pneumonia (9% with acalabrutinib, 10% with idelalisib plus rituximab, and 3% with bendamustine plus rituximab), diarrhea (1%, 16%, and 0%), and pyrexia (3%, 7%, and 3%). The incidence of bleeding events was higher with acalabrutinib than with idelalisib plus rituximab or bendamustine plus rituximab (31%, 8%, and 6%), as was the incidence of atrial fibrillation (8%, 3%, and 3%). Hypertension was reported in 8%, 6%, and 0% of patients, respectively, and major hemorrhage occurred in 3% of patients in all 3 arms.

The investigators concluded that these data show a continued efficacy benefit and a consistent safety profile for acalabrutinib among patients with relapsed/refractory CLL. These data support the long-term use of acalabrutinib in this population, including in patients with high-risk disease.

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# Fixed-Duration Ibrutinib + Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Three-Year Follow-Up From the Fixed-Duration Cohort of the Phase 2 CAPTIVATE Study

The international, multicenter phase 2 CAPTIVATE study evaluated a targeted strategy of ibrutinib plus venetoclax as frontline treatment in patients with CLL who were ages 70 years or younger.[1] The study included a fixed-duration cohort, in which patients received 3 cycles of ibrutinib lead-in followed by 12 cycles of ibrutinib plus venetoclax, and a cohort in which treatment discontinuation was guided by minimal residual disease (MRD). The fixed-duration cohort included 159 patients with previously untreated CLL/SLL requiring treatment, with an Eastern Cooperative Oncology Group performance status of 0 to 2. The primary analysis of the fixed-duration cohort was performed after a median time on study of 27.9 months. The trial met its primary endpoint, with 56% of patients attaining CR/CRi.[1] Response rates were consistent in patients with high-risk features.

At the 2022 ASCO meeting, William G. Wierda, MD, presented an updated analysis from the CAPTIVATE fixed-duration cohort.[2] The patients' median time on study was 38.7 months, including a median of 24.9 months after the end of treatment. The patients' median age was 60 years (range, 33-71), 67% were male, and 86% did not have del(17p). Most patients (92%) completed treatment with ibrutinib and venetoclax. The median treatment duration was 13.8 months, reflecting the planned 15 cycles lasting 28 days each.

In this updated analysis, the CR rate in all treated patients increased from 55% to 57%. The results were similar for the primary endpoint population of patients without del(17p). An estimated 94% of CRs were maintained after 24 months. Among patients with a response, the median duration was not reached. The CR rate was similar among patients with del(17p) or *TP53* mutations (56%) and with unmutated *IGHV* (64%; Figure 7). Undetectable MRD in the blood and/or bone marrow was reported among 79% of patients (125/159). MRD responses appeared to be durable (Figure 8). Among 85 patients with undetectable MRD in the blood at 3 months post-treatment, 66 (78%) maintained undetectable

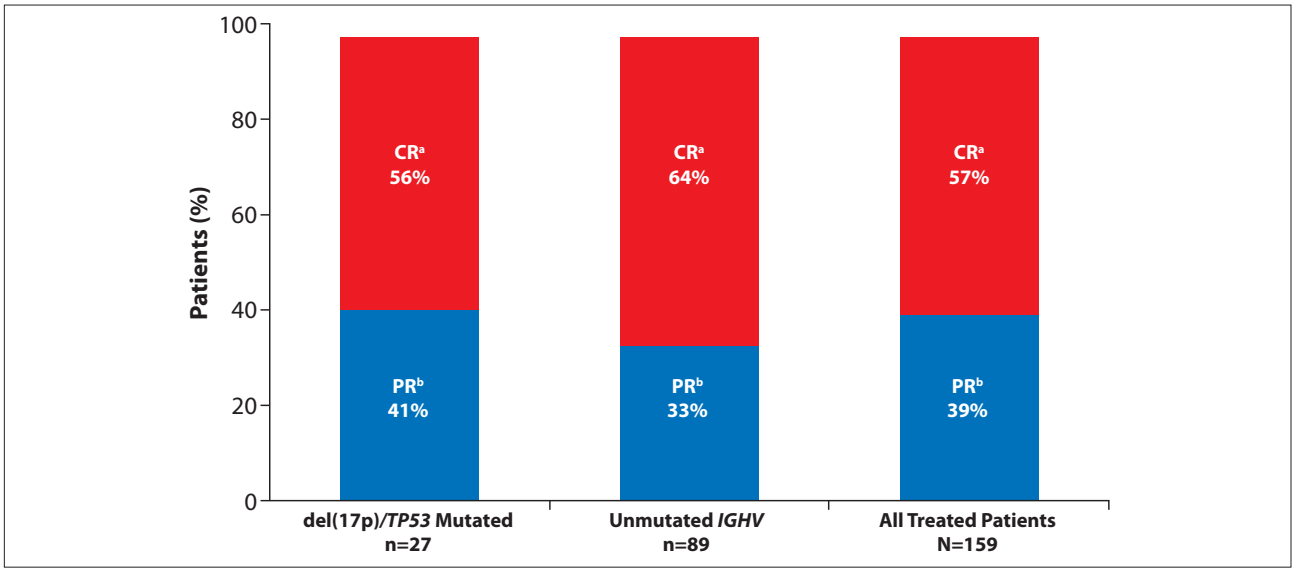


**Figure 7.** Rates of complete response in an updated analysis of the fixed-duration cohort of the phase 2 CAPTIVATE trial, which evaluated ibrutinib plus venetoclax as frontline treatment in patients (≤70 years) with chronic lymphocytic leukemia. [a]The CR rate includes patients with a CR with incomplete bone marrow recovery. [b]The PR rate includes patients with a nodular PR. CR, complete response; del(17p), deletion 17p; *IGHV*, immunoglobulin heavy-chain variable region; PR, partial response. Adapted from Wierda WG et al. ASCO abstract 7519. *J Clin Oncol.* 2022;40(16 suppl).[2]

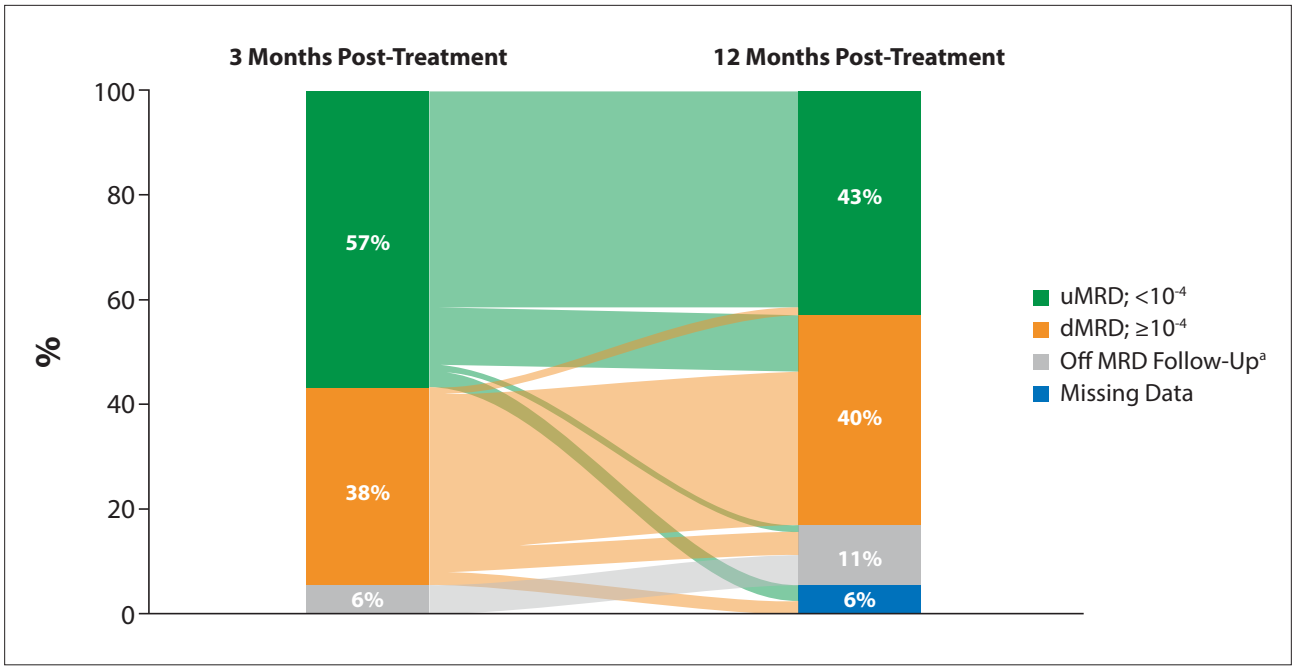


**Figure 8.** Rates of undetectable MRD in the peripheral blood in an updated analysis of the fixed-duration cohort of the phase 2 CAPTIVATE trial, which evaluated ibrutinib plus venetoclax as frontline treatment in patients (≤70 years) with chronic lymphocytic leukemia. dMRD, detectable minimal residual disease; uMRD, undetectable minimal residual disease. [a]Off MRD follow-up included patients who met any one of the following criteria: progressive disease, initiation of subsequent therapy, death, or withdrawal from the study. Adapted from Wierda WG et al. ASCO abstract 7519. *J Clin Oncol.* 2022;40(16 suppl).[2]

levels of MRD through 12 months post-treatment.

The 36-month PFS and OS rates were 88% and 98%, respectively. OS rates were similar among patients with high-risk features. Among 22 patients with disease progression, no *BTK, PLCG2,* or *BCL2* mutations associated with resistance to ibrutinib or venetoclax were detected.

### ABSTRACT SUMMARY Network Meta-Analysis of Progression-Free Survival in the Treatment of Relapsed or Refractory Chronic Lymphocytic Leukemia

A network meta-analysis compared the efficacy of zanubrutinib vs other treatments, including ibrutinib, acalabrutinib, bendamustine plus rituximab, and venetoclax plus rituximab, in patients with relapsed/refractory CLL (Abstract e19514). Data were obtained from 4 randomized controlled trials (ALPINE, ELEVATE-RR, ASCEND, and MURANO). The network meta-analysis suggested that zanubrutinib provides a significant PFS benefit over acalabrutinib (HR, 0.52; 95% CI, 0.30-0.90), ibrutinib (HR, 0.47; 95% CI, 0.29-0.76), and bendamustine plus rituximab (HR, 0.13; 95% CI, 0.06-0.26). There was a trend toward improved PFS with zanubrutinib over venetoclax plus rituximab that was not significant (HR, 0.69; 95% CI, 0.32-1.46). OS analyses showed nonsignificant trends favoring zanubrutinib over acalabrutinib, ibrutinib, and bendamustine plus rituximab, but the investigators cautioned that these findings were uncertain owing to wide confidence intervals.

The most frequent treatment-emergent adverse events (TEAEs) consisted of diarrhea (62%; 3% grade 3), nausea (42%; 1% grade 3), and arthralgia (33%; 1% grade 3). Most TEAEs were grade 1/2 in severity. A notable exception was neutropenia, which occurred in 41% of patients, with 32% developing grade 3/4 cases. Frequent TEAEs generally occurred within 4 months of starting treatment. The median time from onset to resolution or improvement ranged from 16.5 days for diarrhea, to 40.5 days for nausea, to 42.5 days for arthralgia. No new serious AEs or secondary malignancies were reported since the primary analysis.

Twelve patients who developed progressive disease after fixed-duration ibrutinib plus venetoclax were re-treated with single-agent ibrutinib. Treatment led to a partial response in 9 patients and a partial response with lymphocytosis in 1 patient. The study

investigators concluded that treatment with fixed-duration ibrutinib plus venetoclax is an efficacious, oral, once-daily chemotherapy-free fixed-duration regimen for patients with previously untreated CLL/SLL.

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# Four-Year Follow-Up From a Phase 2 Study of Obinutuzumab, Ibrutinib, and Venetoclax in CLL

Clinical trials are evaluating combinations of BTK inhibitors plus the BCL2 inhibitor venetoclax to identify a time-limited, chemotherapy-free treatment regimen. At the 2022 ASCO meeting, Kerry A. Rogers, MD, presented a 4-year follow-up analysis from a phase 2 study evaluating the combination regimen of obinutuzumab, ibrutinib, and venetoclax, administered for up to 14 cycles, among patients with treatment-naive or relapsed/refractory CLL.[1] As reported in 2020, the primary endpoint—the rate of CR with undetectable MRD by flow cytometry in the blood and bone marrow 2 months after completion of treatment—was reached by 28% of patients in both the treatment-naive (n=25) and relapsed/refractory (n=25) cohorts (Figure 9).[2] At the 2022 ASCO meeting, Dr Rogers presented additional data from those 2 cohorts after a median follow-up of approximately 56 months, as well as from a second treatment-naive cohort of 25 patients with a median follow-up of approximately 30 months.

The median age of the enrolled patients was 58 years (range, 24-77 years), and 36% of the patients were female. *IGHV*-unmutated CLL was reported in 75% of patients, and 36% of patients had a complex karyotype. In the relapsed/refractory cohort, the patients had received a median of 1 prior therapy (range, 1-3). Deletion 11q22.3 was detected in 28% of patients, and 8% had del(17p13.1).

At the end of treatment, the ORR was 88% in the relapsed/refractory cohort, 84% in treatment-naive cohort 1, and 96% in treatment-naive cohort 2 (Figure 9). (Among 9 patients [38%] in treatment-naive cohort 2, end-of-treatment assessments were delayed and occurred at a median of 21 weeks, owing to the COVID-19 pandemic.) The median PFS and OS were not reached at the time of the analysis. The estimated rates of 4-year PFS and OS were both 96% for treatment-naive cohort 1, and 85% and 100%, respectively, for the relapsed/refractory cohort. The estimated 2-year PFS and OS rates for treatment-naive cohort 2 were both 96%. During the follow-up period, 3 patients died (1 in each cohort) and 6 patients developed disease progression (4 in the relapsed/refractory cohort and 2 in treatment-naive cohort 1).

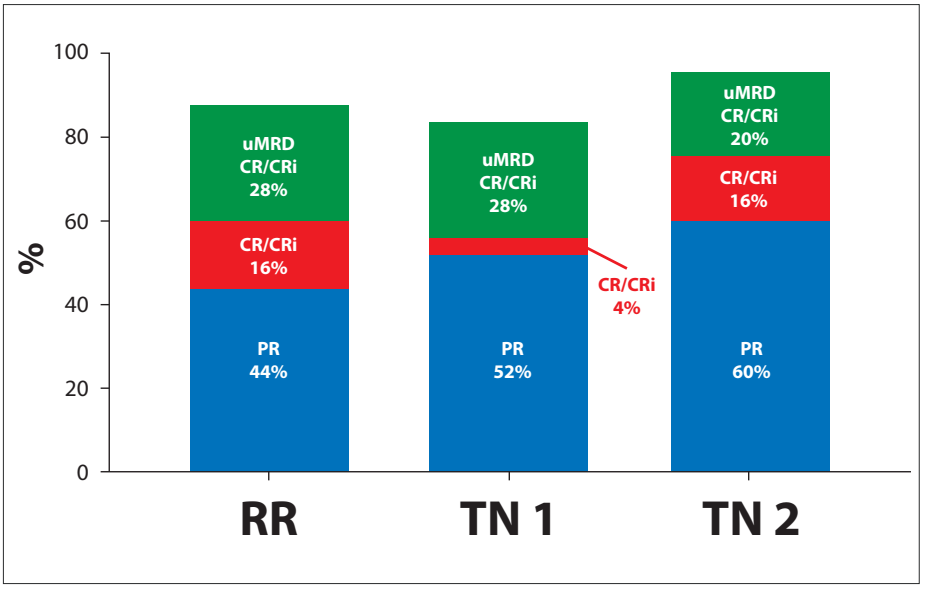


**Figure 9.** Response to treatment according to cohort in a 4-year follow-up analysis of a phase 2 study evaluating the combination of obinutuzumab, ibrutinib, and venetoclax in patients with treatment-naive or relapsed/refractory chronic lymphocytic leukemia. CR, complete remission; CRi, complete remission with incomplete marrow recovery; PR, partial remission; TN, treatment-naive; RR, relapsed/refractory; uMRD, undetectable minimal residual disease. Adapted from Rogers KA et al. ASCO abstract 7540. *J Clin Oncol*. 2022;40(16 suppl).[1]

Assessments conducted at the end of treatment showed MRD negativity in the blood and bone marrow in 50% of patients (11 of 22) in the relapsed/refractory cohort, 67% of patients (14 of 21) in treatment-naive cohort 1, and 65% of patients (10 of 22) in treatment-naive cohort 2. The investigators noted that a substantial proportion of patients had sustained MRD negativity in the blood more than 1 year after completing treatment.

The most common AEs consisted of neutropenia (95% any-grade; 73% grade ≥3), leukopenia (95%; 45%), lymphopenia (93%; 40%), thrombocytopenia (91%; 28%), hypertension (85%; 39%), hypocalcemia (79%; 0%), and diarrhea (77%; 8%). Atrial fibrillation was reported in 11% of patients (8 of 75); grade 3 or higher cases occurred in 3%. Palpitations occurred in 19% of patients. Tumor lysis syndrome and febrile neutropenia each occurred in 1 patient. The investigators stated that based on the demonstrated efficacy and safety of obinutuzumab, ibrutinib, and venetoclax, this regimen is being evaluated as first-line therapy in two phase 3 trials.[3,4]

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# A Phase 1b/2 Study of Lisaftoclax (APG-2575), a Novel BCL2 Inhibitor, in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

The BCL2 inhibitor venetoclax can lead to tumor lysis syndrome. To address this risk, administration incorporates an extended 5-week ramp-up period. Other challenges associated with the use of venetoclax include thrombocytopenia and severe neutropenia.[1] Lisaftoclax is a novel BCL2 inhibitor in development. In a first-in-human study of lisaftoclax, a daily ramp-up schedule appeared to be feasible.[2]

At the 2022 ASCO meeting, Jianyong Li, MD, PhD, presented results of a multicenter open-label phase 1b/2 trial evaluating lisaftoclax in patients with relapsed/refractory CLL/SLL in China.[3] Lisaftoclax was administered orally once daily at 400 mg, 600 mg, or 800 mg, with 15 patients in each cohort. Overall, the median age of the 45 enrolled patients was 58 years (range, 38-80), 76% were male, 20% had complex chromosomal abnormalities, and 33% had del(17p)/*TP53* mutations.

Lisaftoclax was generally well tolerated at doses up to 800 mg per day, with no dose-limiting toxicities. The maximum tolerated dose was not

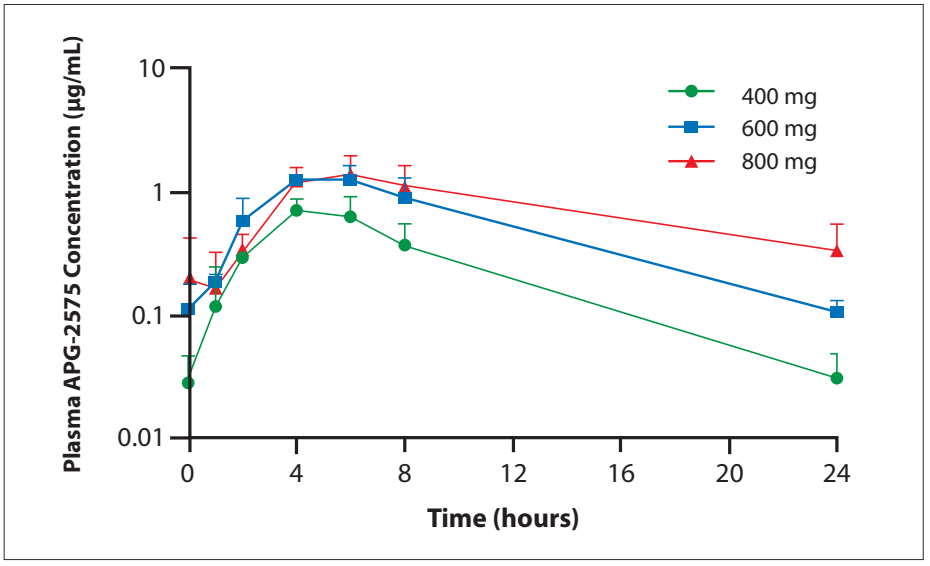


**Figure 10.** The steady state concentration-time profile of lisaftoclax (APG-2575) in a phase 1b/2 study. Adapted from Li J et al. ASCO abstract 7543. *J Clin Oncol.* 2022;40(16 suppl).[3]

reached. A pharmacokinetics analysis found an approximately dose-proportional increase in exposure at dose levels of 400 mg to 800 mg (Figure 10).

Grade 3 or higher TEAEs were reported in 56% of patients, and 20% of patients developed treatment-emergent serious AEs. Fourteen patients (31%) discontinued treatment, with no discontinuations owing to TEAEs. The most frequent TEAEs of any grade included neutrophil count decrease (56%), anemia (42%), white blood cell count decrease (40%), platelet count decrease (38%), hyperuricemia (31%), hypokalemia (24%), blood bilirubin increase (22%), diarrhea (20%), and hypertriglyceridemia (20%). The most frequent grade 3 or higher TEAEs were neutrophil count decrease (31%), platelet count decrease (24%), and anemia (9%). One case of clinical tumor lysis syndrome was reported.

After a median of 7 cycles, lisaftoclax was associated with an ORR of 67%, with 1 CR (2%). The median time to response was 1 cycle (range, 1-13). The recommended phase 2 dose of single-agent lisaftoclax was identified as 600 mg. The investigators concluded that lisaftoclax may offer an alternative for the treatment of relapsed/refractory CLL/SLL that provides a more patient-friendly daily ramp-up schedule.

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# Phase 1/2 Study of Zilovertamab and Ibrutinib in Mantle Cell Lymphoma or Chronic Lymphocytic Leukemia

Zilovertamab is a humanized monoclonal antibody that is directed against ROR1, an onco-embryonic tyrosine kinase–like receptor that is expressed in hematologic cancers, including CLL, but not in healthy adult tissues. At the 2022 ASCO meeting, Hun Ju Lee, MD, presented results of a phase 1/2 study evaluating the combination of zilovertamab (previously known as cirmtuzumab) and ibrutinib in patients with MCL or CLL.[1] The dose-finding cohort, which included 18 patients with CLL, evaluated a range of zilovertamab doses, with ibrutinib added after 1 month. The dose-expansion cohort, which included 16 patients with CLL, confirmed the recommended zilovertamab dose of 600 mg, which was administered with ibrutinib at approved doses. Another 31 patients with CLL were enrolled in a phase 2 randomized cohort that compared zilovertamab plus ibrutinib (n=18) with ibrutinib alone (n=10). Among the patients with CLL enrolled across the study cohorts, the median age was 66 to 68 years. The patients had received a median of 2 prior systemic regimens (range, 1-9).

The regimen was generally well tolerated, with a safety profile similar to ibrutinib alone. Among patients with CLL who received zilovertamab plus ibrutinib in the dose-finding and dose-expansion cohorts, the most frequent TEAEs of any grade included platelet decrease (74%), hemoglobin decrease (74%), neutropenia (47%), contusion (47%), hypertension (47%), diarrhea (44%), upper respiratory tract infection (44%), fatigue (41%), muscle spasms (32%), and onycholysis (32%). The most common grade 3 or higher TEAEs included hypertension (21%), neutropenia (18%), and diarrhea (6%). In the randomized controlled cohort, the most common TEAEs of any grade reported with zilovertamab plus ibrutinib and ibrutinib alone were hemoglobin decrease (occurring in 89% vs 70%, respectively), platelet decrease (72% vs 80%), contusion (39% vs 40%), neutropenia (33% vs 30%), back pain (33% vs 40%), and fatigue (33% vs 30%). The grade 3 or higher TEAEs reported in more than 1 patient receiving zilovertamab plus ibrutinib consisted of back pain (2 patients; 11%) and pneumonia (2 patients; 11%). The most common grade 3 or higher TEAEs in patients receiving ibrutinib alone were pneumonia (2 patients; 20%) and neutropenia (2 patients; 20%).

Clinical responses were observed among heavily pretreated patients with CLL. In the dose-finding and dose-expansion cohorts, zilovertamab plus ibrutinib was associated with an ORR of 91% (including a CR rate of 9%) in the overall population (n=34) and 88% (all partial responses) in patients who had received 3 or more prior regimens (n=8). In the randomized cohort, the ORR was 94% (all partial responses) with zilovertamab plus ibrutinib and 100% (all partial responses) with ibrutinib monotherapy. Responses were observed in pretreated patients. The median response duration was 33.5 months in the dose-finding and dose-expansion cohorts, and not reached in the randomized cohort.

The median PFS was not reached in any study cohort after a median

follow-up ranging from 24 months to 33.5 months. The median PFS was also not reached among patients with *TP53* mutations after a median follow-up duration of at least 33 months. The median PFS was not reached in treatment-naive patients or in those treated with 1 or 2 prior regimens. The median PFS was 36 months among those who had received 3 or more prior regimens. Among the previously treated patients, landmark 3-year PFS rates with zilovertamab plus ibrutinib were approximately 100% in patients who had received 1 or 2 prior regimens and approximately 70% in patients who had received more than 2 prior regimens. The study investigators noted that these data compare favorably to historical control data for ibrutinib monotherapy, in which 3-year PFS rates were approximately 73% in patients who had received 1 to 2 prior regimens and approximately 50% in those who had received more than 2 prior regimens.[2] The median OS was not reached in any CLL cohort.

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# Phase 1 Dose Escalation of LAVA-051, a Novel Bispecific Gamma-Delta T-Cell Engager (Gammabody), in Relapsed/Refractory Hematologic Malignancies

The novel bispecific γδ T-cell engager LAVA-051 targets CD1D, which is expressed in CLL and multiple myeloma cells, and the Vδ2 T-cell receptor chain of Vg9Vδ2 T cells, an innate-like T-cell population with antitumor activity. Preclinical data suggest that LAVA-051 has a low potential for inducing cytokine release syndrome, and therefore is expected to have a broad therapeutic window.[1] At the 2022 ASCO meeting, Annemiek Broijl, MD, PhD, presented results of a phase 1 dose-escalation study of LAVA-051 in a small cohort of 3 patients with CLL and 3 patients with multiple myeloma.[1]

Using an open-label, accelerated titration design, the study evaluated a range of LAVA-051 doses administered via intravenous infusion or subcutaneous injection. The 3 patients with CLL had received between 3 and 5 prior therapies. As of the analysis, the starting dose of LAVA-051 had been increased by 100-fold in both disease cohorts. There were no cases of cytokine release syndrome or immune effector cell–associated neurotoxicity syndrome, or of significant increases in levels of interleukin 6. No dose-limiting toxicities were reported. No patients developed anti-drug antibodies. Most observed AEs were not considered treatment-related. No grade 2 or higher TEAEs were reported in more than 1 patient. One patient developed a grade 2 infusion-related reaction, and 1 patient developed grade 3 neutropenia.

The investigators noted that the drug's pharmacodynamic parameters reflected the mechanism of action. The concentration of Vg9Vδ2 in the peripheral blood decreased early after drug administration but subsequently recovered. Administration of LAVA-051 was associated with consistent increased expression of the activation markers CD25 and CD69, indicating activation of Vg9Vδ2 T-cells. Moreover, there was a dose-dependent increase in Vg9Vδ2 T-cell receptor occupancy with increasing LAVA-051 doses. In this early analysis, there were potential signs of antitumor activity, including signs of a tumor flare reaction and a reduction in the percentage of clonal B cells in the blood in a patient with CLL who had stable disease. The patient stopped treatment after cycle 5 owing to a COVID diagnosis. Clinical investigations of LAVA-051 are ongoing.

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# Highlights in Chronic Lymphocytic Leukemia From the 2022 American Society of Clinical Oncology Annual Meeting: Commentary

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At the 2022 American Society of Clinical Oncology (ASCO) annual meeting, several presentations evaluated treatments for chronic lymphocytic leukemia (CLL). Follow-up analyses of phase 3 trials provided long-term data for the Bruton's tyrosine kinase (BTK) inhibitor acalabrutinib. Another follow-up analysis evaluated fixed-duration treatment with venetoclax and ibrutinib. Two network meta-analyses compared data for BTK inhibitors and other treatments. Another important study provided insights into the epidemiology of the disease.

## The Influence of Racial and Ethnic Identity on Overall Survival in CLL

Dr Daniel Ermann and colleagues presented interesting results of a study that examined the influence of racial and ethnic identity on overall survival in patients with CLL.[1] The field of CLL needs more real-world data, as well as data evaluating disparities in care and outcome among various subgroups of patients. This retrospective review examined records from the National Cancer Database (NCDB) and identified approximately 97,800 patients who were diagnosed with CLL from 2004 to 2018. The aim was to evaluate outcomes for patients based on their racial groups, such as White, Black, Asian, and Hispanic. The first noteworthy observation from the study was that approximately 90% of the patients in the database were White. Black and Hispanic patients constituted a small subset of patients with CLL. This finding is consistent with previous studies showing that CLL is predominantly a disease of older White men.[2] The analysis provides evidence to support observations from clinical experience and previous reports suggesting that outcome is worse in Black patients.[3-5] The median age at diagnosis was 66 years for Black patients vs 70 years for White patients. Black patients had a higher burden of comorbidity at diagnosis and were more likely to be uninsured.

There were other important findings in this analysis. Treatment for CLL is typically initiated once patients develop disease progression that causes symptoms or abnormalities in blood counts, lymph nodes, or the spleen. Black patients were more likely than white patients to begin early treatment. Treatment began immediately after diagnosis in 35% of Black patients vs 23% of White patients.[1] This difference might reflect the type of settings in which Black patients tend to seek care. More importantly, Black patients might have more aggressive disease that requires earlier treatment.

The most important finding of this analysis was that overall survival was much worse in Black patients as compared with all other ethnic groups, including White and Hispanic patients. The median overall survival was 7 years for Black patients, 9.1 years for White patients, and 10.4 years for Hispanic patients. A multivariate analysis found that Black ethnicity was independently associated with poor outcomes. There was no other variable that could explain why these patients did poorly. Essentially all outcomes were significantly worse among Black patients compared with the other ethnic groups.

Studies in cancers consistently show that Black patients have worse outcomes than other racial groups.[6,7] This analysis highlights a need in CLL that community awareness organizations and clinicians can address. Hopefully, it will be possible to improve outcomes for patients across all ethnic and racial groups.

## Acalabrutinib

At the 2022 ASCO meeting, investigators presented updates for 2 studies of acalabrutinib in CLL. The large, randomized phase 3 ELEVATE-TN trial evaluated acalabrutinib alone, acalabrutinib plus obinutuzumab, and chlorambucil plus obinutuzumab in patients with previously untreated CLL.[8] The study randomly assigned 535 patients into 3 groups. Group 1 received acalabrutinib alone (n=179). Group 2 received acalabrutinib plus obinutuzumab (n=179). Group 3 received chlorambucil plus obinutuzumab (n=177). Initial reports of the ELEVATE-TN study showed

improved outcomes among patients in the acalabrutinib arms compared with those in the chlorambucil/obinutuzumab arm.[8] Dr Jeff Sharman and colleagues presented results from an updated 5-year analysis, which continued to show that outcomes were superior in the acalabrutinib arms.[9] An important finding from this analysis was that patients who received acalabrutinib plus obinutuzumab had better outcomes compared with patients who received acalabrutinib alone. The ELEVATE-TN study was not designed to detect a difference between the 2 acalabrutinib-containing arms. However, these data indirectly answer an important question in the field, which is whether the addition of a CD20 antibody to a BTK inhibitor improves long-term outcomes. The rate of progression-free survival (PFS) at 5 years was 72% with acalabrutinib alone vs 84% with acalabrutinib plus obinutuzumab. This improvement in PFS was noted in the earlier reports and has continued to increase over the years, suggesting that combining BTK inhibitors with obinutuzumab might be an effective and viable strategy.

There were no new safety signals or adverse events reported in the updated analysis.[9] The toxicities in both acalabrutinib arms were expected. They included bleeding and headache. Atrial fibrillation, an adverse event of interest, occurred at fairly similar rates in the acalabrutinib arms (6.2% with acalabrutinib plus obinutuzumab, 7.3% with acalabrutinib alone, and 0.6% with obinutuzumab plus chlorambucil).

This important 5-year analysis of the ELEVATE-TN study provides promising data.[9] Throughout the COVID-19 pandemic, physicians aimed to minimize the use of CD20 antibodies because of the associated risk of infectious complications. In the future, however, it may be possible to justify this risk based on the long-term improvement in PFS. It remains to be seen whether the addition of obinutuzumab to acalabrutinib will become the standard of care.

Dr Wojciech Jurczak and colleagues presented data from a 4-year follow-up analysis of the ASCEND trial, which evaluated acalabrutinib in 310 patients with relapsed/refractory CLL.[10,11] The trial compared acalabrutinib (n=155) vs idelalisib plus rituximab (n=119) or bendamustine plus rituximab (n=36). Earlier results showed a significant improvement in PFS among patients treated with acalabrutinib vs those treated with idelalisib plus rituximab or bendamustine plus rituximab.[10] This significant improvement in PFS was maintained in the 4-year analysis.[11] The median PFS was not reached in the acalabrutinib arm vs 16.8 months in the control arm.

Importantly, this analysis also showed that acalabrutinib significantly improved outcome among patients with deletion 17p (del[17p]). In the acalabrutinib arm, the median PFS was not reached for patients with or without del(17p). Other treatments, notably venetoclax, are less effective in patients with del(17p).[12] In the ASCEND study, among patients treated with idelalisib plus rituximab or bendamustine plus rituximab, the median PFS was 20.3 months for patients without del(17p) and 13.8 months for patients with del(17p).

This analysis of the ASCEND trial raised another important point. No head-to-head trial has compared a BTK inhibitor and a phosphoinositide 3-kinase (PI3K) inhibitor in patients with CLL. There has been some debate regarding the relative efficacy of a BTK inhibitor compared with a PI3K inhibitor. The ASCEND trial did not address this question directly. However, the trial provides a comparison between a fairly large group comprising patients treated with idelalisib plus rituximab and a smaller group of patients treated with bendamustine plus rituximab. These treatments led to similar outcomes, and acalabrutinib was shown to be superior to both.

In the modern era, it is difficult to demonstrate an improvement in overall survival among patients with CLL. Patients have access to many effective therapies, and if one therapy is unsuccessful, another novel therapy is utilized. Therefore, in this analysis of the ASCEND trial, acalabrutinib did not significantly improve overall survival. However, there was a trend toward improvement.

Treatment with BTK inhibitors must be continued indefinitely, which can be challenging if patients develop problematic side effects. Chemotherapy can be stopped after 6 months. An important finding of this analysis was that the rate of adverse events, including infections, was significantly lower in the acalabrutinib arm vs the control arms and fairly similar to previous reports.[10] This 4-year analysis of the ASCEND trial shows promising results for acalabrutinib in the setting of relapsed/refractory CLL.

## Network Meta-Analyses

Dr Asher Chanan-Khan and colleagues provided data from studies that can be considered surrogates for clinical trials.[13,14] Generating data for direct comparisons of BTK inhibitors with various available therapeutic options requires large, randomized trials that take years to complete. There are data available from 2 head-to-head trials comparing acalabrutinib and zanubrutinib, respectively, with ibrutinib.[15,16] However, given the similar efficacy and variable toxicity results, it is difficult to identify the best option among the various treatments that are available. To address the question of which BTK inhibitor is potentially the best, Dr Chanan-Khan and colleagues performed 2 network meta-analyses of trials that evaluated the most common treatments in CLL.[13,14] An analysis of treatment-naive patients included trials evaluating zanubrutinib; ibrutinib; bendamustine plus rituximab; chlorambucil plus obinutuzumab; and

chlorambucil plus rituximab. Among patients with relapsed/refractory disease, the trials evaluated zanubrutinib; ibrutinib; acalabrutinib; bendamustine plus rituximab; and venetoclax plus rituximab.

In the analysis of patients in the frontline setting, there was a statistically significant improvement in PFS with the use of zanubrutinib vs bendamustine plus rituximab.[13] Zanubrutinib was also superior to chlorambucil plus obinutuzumab and chlorambucil plus rituximab. PFS was comparable between zanubrutinib and ibrutinib. It should be stated that cross-trial comparisons typically should not be considered proof that one treatment is better than another. However, this analysis suggests that the efficacy of BTK inhibitors is fairly similar and superior to the alternative options, such as bendamustine plus rituximab.

The meta-analysis of studies in the relapsed/refractory setting showed that zanubrutinib significantly improved PFS as compared with acalabrutinib, ibrutinib, and bendamustine/rituximab.[14] There was a trend toward improved PFS for zanubrutinib compared with venetoclax plus rituximab, although the difference did not reach statistical significance.

These types of analyses, although not traditional phase 3 randomized clinical trials, provide evidence that can inform treatment selection. However, an important element missing from these analyses was an examination of toxicity. Agents might have similar efficacy, but different rates of adverse events. It would be difficult to justify switching treatment to an agent with similar efficacy but higher toxicity. If a meta-analysis were to demonstrate that a particular agent improved efficacy with better tolerability, this finding could be considered a compelling reason to use this agent, even in the absence of randomized clinical trial data.

## Ibrutinib Plus Venetoclax

The multicenter phase 2 CAPTIVATE study evaluated ibrutinib plus venetoclax for the frontline treatment of patients with CLL.[17] Dr William Wierda and colleagues presented 3-year follow-up data from the fixed-duration cohort (n=159).[18] Previous reports of the CAPTIVATE study showed that frontline treatment with ibrutinib and venetoclax is very effective.[17] This regimen is also effective in the relapsed/refractory setting.[19] In the fixed-duration cohort of the CAPTIVATE study, ibrutinib was administered as a lead-in drug for the first 3 cycles. Venetoclax was then administered, using the standard ramp-up dose, along with concomitant ibrutinib. Combination therapy was given for 12 months, for a total treatment duration of 15 months. Subsequently, patients with progressive disease could receive re-treatment with single-agent ibrutinib. Patients with a durable response could receive fixed-duration ibrutinib plus venetoclax.

Previous data showed that this regimen had a very high success rate in terms of depth of response.[17] In this analysis, all patients had good outcomes with the use of ibrutinib and venetoclax. The 3-year rate of PFS was 88%. This outcome is comparable with other studies of BTK inhibitors, which have shown a 4-year PFS rate of approximately 80%.[8] Undetectable minimal residual disease as measured in the peripheral blood or bone marrow biopsy was reported in 79% of patients.[18] These promising results also showed good tolerability of the fixed-duration treatment.

The study analyzed outcome according to high-risk subtypes. Immunoglobulin heavy-chain variable region (IGHV) mutational status did not appear to impact outcome. Patients with del(17p) or *TP53* mutations had a slightly inferior outcome as compared with patients without these abnormalities.

This analysis of the fixed-duration cohort also evaluated outcome when patients stopped treatment after 15 months.[18] Among the 159 patients in this cohort, 26 patients developed progressive disease. The rate of disease progression was fairly low, and progression did not appear to impact overall survival. Twelve of the patients who progressed after fixed-duration therapy received further treatment with single-agent ibrutinib. Ten of these patients had a partial response, and 1 patient had stable disease. (Outcome was unavailable for 1 patient.)

This analysis highlights several findings. A finite duration of treatment can result in deep responses. A substantial percentage of these patients may not require treatment for a fairly long

**ABSTRACT SUMMARY Efficacy of First-Line Treatment for Chronic Lymphocytic Leukemia: A Bayesian Network Meta-Analysis**

A Bayesian network meta-analysis compared the efficacy of zanubrutinib vs ibrutinib, bendamustine plus rituximab, chlorambucil plus obinutuzumab, and chlorambucil plus rituximab for the first-line treatment of CLL (Abstract e19526). Data were analyzed from 4 randomized controlled trials: CLL11, ALLIANCE, MABLE, and SEQUOIA. A feasibility assessment was performed to ensure that the trials did not differ with respect to relevant factors including age and the presence of mutations, such as del(11) and del(17). A Bayesian network meta-analysis showed a significant PFS benefit with zanubrutinib compared with bendamustine plus rituximab (HR, 0.42; 95% CI, 0.27-0.65), chlorambucil plus obinutuzumab (HR, 0.45; 95% CI, 0.23-0.86), and chlorambucil plus rituximab (HR, 0.22; 95% CI, 0.12-0.41). PFS was comparable between zanubrutinib and ibrutinib (HR, 1.07; 95% CI, 0.59-1.94).

period. When treatment is needed, single-agent ibrutinib is effective.

Toxicities can be a concern with the doublet of ibrutinib plus venetoclax. The predominant adverse events consisted of neutropenia, diarrhea, arthralgia, and nausea.[18] Ibrutinib is associated with a significant incidence of cardiovascular side effects,[21] which can be an issue for patients who restart ibrutinib after the initial 15 months of therapy. However, these results from the CAPTIVATE study show that CLL can be controlled for a fairly long period with a finite duration of therapy.

### *Disclosure*

*Dr Awan has provided consultancy services to Genentech, AstraZeneca, AbbVie, Janssen, Pharmacyclics, Gilead Sciences, Kite Pharma, Celgene, Karyopharm, MEI Pharma, Verastem, Incyte, BeiGene, Johnson & Johnson, DAVA Oncology, BMS, Merck, Cardinal Health, ADC Therapeutics, Epizyme, and Caribou Biosciences. He has received research funding from Pharmacyclics.*

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**CALQUENCE® (acalabrutinib) capsules, for oral use**
**Initial U.S. Approval: 2017**

*Brief Summary of Prescribing Information.*
*For full Prescribing Information consult official package insert.*

## INDICATIONS AND USAGE

**Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma**
CALQUENCE is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

## DOSAGE AND ADMINISTRATION

**Recommended Dosage**

CALQUENCE as Monotherapy

For patients with CLL or SLL, the recommended dose of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.

CALQUENCE in Combination with Obinutuzumab

For patients with previously untreated CLL or SLL, the recommended dose of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. Start CALQUENCE at Cycle 1 (each cycle is 28 days). Start obinutuzumab at Cycle 2 for a total of 6 cycles and refer to the obinutuzumab prescribing information for recommended dosing. Administer CALQUENCE prior to obinutuzumab when given on the same day.

Advise patients to swallow capsule whole with water. Advise patients not to open, break or chew the capsules. CALQUENCE may be taken with or without food. If a dose of CALQUENCE is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time.

Extra capsules of CALQUENCE should not be taken to make up for a missed dose.

**Recommended Dosage for Hepatic Impairment**
Avoid administration of CALQUENCE in patients with severe hepatic impairment.

Dose modifications are not required for patients with mild or moderate hepatic impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

**Recommended Dosage for Drug Interactions**

Dose Modifications for Use with CYP3A Inhibitors or Inducers

These are described in Table 1 *[see Drug Interactions (7) in the full Prescribing Information]*.

**Table 1: Recommended Dose Modifications for Use with CYP3A Inhibitors or Inducers**

| CYP3A | Co-administered Drug | Recommended CALQUENCE use |
|---|---|---|
| Inhibition | Strong CYP3A inhibitor | Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE. |
| | Moderate CYP3A inhibitor | 100 mg once daily. |
| Induction | Strong CYP3A inducer | Avoid concomitant use. If these inducers cannot be avoided, increase CALQUENCE dose to 200 mg approximately every 12 hours. |

Concomitant Use with Gastric Acid Reducing Agents

*Proton Pump Inhibitors:* Avoid concomitant use *[see Drug Interactions (7) in the full Prescribing Information]*.

*H2-Receptor Antagonists:* Take CALQUENCE 2 hours before taking a H2-receptor antagonist *[see Drug Interactions (7) in the full Prescribing Information]*.

Antacids: Separate dosing by at least 2 hours *[see Drug Interactions (7) in the full Prescribing Information]*.

**Dose Modifications for Adverse Reactions**
Recommended dose modifications of CALQUENCE for Grade 3 or greater adverse reactions are provided in Table 2.

**Table 2: Recommended Dose Modifications for Adverse Reactions**

| Event | Adverse Reaction Occurrence | Dose Modification (Starting dose = 100 mg approximately every 12 hours) |
|---|---|---|
| Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days | First and Second | Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at 100 mg approximately every 12 hours. |
| | Third | Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at a reduced frequency of 100 mg once daily. |
| | Fourth | Discontinue CALQUENCE. |

Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

Refer to the obinutuzumab prescribing information for management of obinutuzumab toxicities.

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

**Serious and Opportunistic Infections**
Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE.

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Opportunistic infections in recipients of CALQUENCE have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, *Pneumocystis jiroveci* pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

**Hemorrhage**
Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.

Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 2.7% of patients taking CALQUENCE without antithrombotic agents and 3.6% of patients taking CALQUENCE with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding.

Consider the benefit-risk of withholding CALQUENCE for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

**Cytopenias**
Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dose Modifications for Adverse Reactions (2.4) in the full Prescribing Information]*.

**Second Primary Malignancies**
Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE in clinical trials. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

**Atrial Fibrillation and Flutter**
Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

## ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious and Opportunistic Infections *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Hemorrhage *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Cytopenias *[see Warnings and Precautions (5.3) in the full Prescribing Information]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Atrial Fibrillation and Flutter *[see Warnings and Precautions (5.5) in the full Prescribing Information]*

**Clinical Trials Experience**
As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions reflect exposure to CALQUENCE 100 mg approximately every 12 hours in 1029 patients with hematologic malignancies. Treatment includes CALQUENCE monotherapy in 820 patients in 6 trials, and CALQUENCE with obinutuzumab in 209 patients in 2 trials. Among these recipients of CALQUENCE, 88% were exposed for at least 6 months and 79% were exposed for at least one year. In this pooled safety population, adverse reactions in ≥ 30% of 1029 patients were anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain.

Chronic Lymphocytic Leukemia

The safety data described below reflect exposure to CALQUENCE (100 mg approximately every 12 hours, with or without obinutuzumab) in 511 patients with CLL from two randomized controlled clinical trials *[see Clinical Studies (14.2) in the full Prescribing Information]*.

The most common adverse reactions (≥ 30%) of any grade in patients with CLL were anemia, neutropenia, thrombocytopenia, headache, upper respiratory tract infection, and diarrhea.

*ELEVATE-TN*
The safety of CALQUENCE plus obinutuzumab (CALQUENCE+G), CALQUENCE monotherapy, and obinutuzumab plus chlorambucil (GClb) was evaluated in a randomized, multicenter, open-label, actively controlled trial in 526 patients with previously untreated CLL *[see Clinical Studies (14.2) in the full Prescribing Information]*.

Patients randomized to the CALQUENCE+G arm were treated with CALQUENCE and obinutuzumab in combination for six cycles, then with CALQUENCE as monotherapy until disease progression or unacceptable toxicity. Patients initiated obinutuzumab on Day 1 of Cycle 2, continuing for a total of 6 cycles. Patient randomized to CALQUENCE monotherapy received CALQUENCE approximately every 12 hours until disease progression or unacceptable toxicity. The trial required age ≥ 65 years of age or 18 to < 65 years of age with a total Cumulative Illness Rating Scale (CIRS) > 6 or creatinine clearance of 30 to 69 mL/min, hepatic transaminases ≤ 3 times upper limit of normal (ULN) and total bilirubin ≤ 1.5 times ULN, and allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists.

During randomized treatment, the median duration of exposure to CALQUENCE in the CALQUENCE+G and CALQUENCE monotherapy arms was 27.7 months (range 0.3 to 40 months), with 95% and 92% and 89% and 86% of patients with at least 6 months and 12 months of exposure, respectively. In the obinutuzumab and chlorambucil arm the median number of cycles was 6 with 84% of patients receiving at least 6 cycles of obinutuzumab, 70% of patients received at least 6 cycles of chlorambucil. Eighty-five percent of patients in the CALQUENCE+G arm received at least 6 cycles of obinutuzumab.

In the CALQUENCE+G and CALQUENCE monotherapy arms, fatal adverse reactions that occurred in the absence of disease progression and with onset within 30 days of the last study treatment were reported in 2% for each treatment arm, most often from infection. Serious adverse reactions were reported in 39% of patients in the CALQUENCE+G arm and 32% in the CALQUENCE monotherapy arm, most often due to events of pneumonia (2.8% to 7%).

In the CALQUENCE+G arm, adverse reactions led to treatment discontinuation in 11% of patients and a dose reduction of CALQUENCE in 7% of patients. In the CALQUENCE monotherapy arm, adverse reactions led to discontinuation in 10% and dose reduction in 4% of patients.

Tables 5 and 6 presents adverse reactions and laboratory abnormalities identified in the ELEVATE-TN trial.

**Table 5: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE in Patients with CLL (ELEVATE-TN)**

| Body System Adverse Reaction* | CALQUENCE plus Obinutuzumab N=178 | | CALQUENCE Monotherapy N=179 | | Obinutuzumab plus Chlorambucil N=169 | |
|---|---|---|---|---|---|---|
| | All Grades (%) | Grade ≥ 3 (%) | All Grades (%) | Grade ≥ 3 (%) | All Grades (%) | Grade ≥ 3 (%) |
| **Infections** | | | | | | |
| Infection† | 69 | 22‡ | 65 | 14‡ | 46 | 13‡ |
| Upper respiratory tract infection[a] | 39 | 2.8 | 35 | 0 | 17 | 1.2 |
| Lower respiratory tract infection[b] | 24 | 8 | 18 | 4.5 | 7 | 1.8 |
| Urinary tract infection | 15 | 1.7 | 15 | 2.8 | 5 | 0.6 |
| **Blood and lymphatic system disorders§** | | | | | | |
| Neutropenia[c] | 53 | 37 | 23 | 13 | 78 | 50 |
| Anemia[d] | 52 | 12 | 53 | 10 | 54 | 14 |
| Thrombocytopenia[e] | 51 | 12 | 32 | 3.4 | 61 | 16 |
| Lymphocytosis[f] | 12 | 11 | 16 | 15 | 0.6 | 0.6 |
| **Nervous system disorders** | | | | | | |
| Headache | 40 | 1.1 | 39 | 1.1 | 12 | 0 |
| Dizziness | 20 | 0 | 12 | 0 | 7 | 0 |
| **Gastrointestinal disorders** | | | | | | |
| Diarrhea | 39 | 4.5 | 35 | 0.6 | 21 | 1.8 |
| Nausea | 20 | 0 | 22 | 0 | 31 | 0 |
| **Musculoskeletal and connective tissue disorders** | | | | | | |
| Musculoskeletal pain[g] | 37 | 2.2 | 32 | 1.1 | 16 | 2.4 |
| Arthralgia | 22 | 1.1 | 16 | 0.6 | 4.7 | 1.2 |
| **General disorders and administration site conditions** | | | | | | |
| Fatigue[h] | 34 | 2.2 | 23 | 1.1 | 24 | 1.2 |
| **Skin and subcutaneous tissue disorders** | | | | | | |
| Bruising[i] | 31 | 0 | 21 | 0 | 5 | 0 |
| Rash[j] | 26 | 2.2 | 25 | 0.6 | 9 | 0.6 |
| **Vascular disorders** | | | | | | |
| Hemorrhage[k] | 20 | 1.7 | 20 | 1.7 | 6 | 0 |

* Per NCI CTCAE version 4.03
† Includes any adverse reactions involving infection or febrile neutropenia

‡ Includes 3 fatal cases in the CALQUENCE plus obinutuzumab arm, 3 fatal cases in the CALQUENCE monotherapy arm and 1 fatal case in the obinutuzumab plus chlorambucil arm
§ Derived from adverse reaction and laboratory data
[a] Upper respiratory tract infection, nasopharyngitis and sinusitis
[b] Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection
[c] Includes neutropenia, neutrophil count decreased, and related laboratory data
[d] Includes anemia, red blood cell count decreased, and related laboratory data
[e] Includes thrombocytopenia, platelet count decreased, and related laboratory data
[f] Includes lymphocytosis, lymphocyte count increased, and related laboratory data
[g] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain
[h] Includes asthenia, fatigue, and lethargy
[i] Includes bruise, contusion, and ecchymosis
[j] Includes rash, dermatitis, and other related terms
[k] Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE (CALQUENCE in combination with obinutuzumab and monotherapy) included:

- *Neoplasms:* second primary malignancy (10%), non-melanoma skin cancer (5%)
- *Cardiac disorders:* atrial fibrillation or flutter (3.6%), hypertension (5%)
- *Infection:* herpesvirus infection (6%)

**Table 6: Select Non-Hematologic Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ELEVATE-TN)**

| Laboratory Abnormality*,[a] | CALQUENCE plus Obinutuzumab N=178 | | CALQUENCE Monotherapy N=179 | | Obinutuzumab plus Chlorambucil N=169 | |
|---|---|---|---|---|---|---|
| | All Grades (%) | Grade ≥ 3 (%) | All Grades (%) | Grade ≥ 3 (%) | All Grades (%) | Grade ≥ 3 (%) |
| **Uric acid increase** | 29 | 29 | 22 | 22 | 37 | 37 |
| **ALT increase** | 30 | 7 | 20 | 1.1 | 36 | 6 |
| **AST increase** | 38 | 5 | 17 | 0.6 | 60 | 8 |
| **Bilirubin increase** | 13 | 0.6 | 15 | 0.6 | 11 | 0.6 |

*Per NCI CTCAE version 4.03
[a] Excludes electrolytes

Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 3.9% and 2.8% of patients in the CALQUENCE combination arm and monotherapy arm, respectively.

*ASCEND*

The safety of CALQUENCE in patients with relapsed or refractory CLL was evaluated in a randomized, open-label study (ASCEND) *[see Clinical Studies (14.2) in the full Prescribing Information]*. The trial enrolled patients with relapsed or refractory CLL after at least one prior therapy and required hepatic transaminases ≤ 2 times upper limit of normal (ULN), total bilirubin ≤ 1.5 times ULN, and an estimated creatinine clearance ≥ 30 mL/min. The trial excluded patients having an absolute neutrophil count < 500/µL, platelet count < 30,000/µL, prothrombin time or activated partial thromboplastin time > 2 times ULN, significant cardiovascular disease, or a requirement for strong CYP3A inhibitors or inducers. Patients were allowed to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonist.

In ASCEND, 154 patients received CALQUENCE (100 mg approximately every 12 hours until disease progression or unacceptable toxicity), 118 received idelalisib (150 mg approximately every 12 hours until disease progression or unacceptable toxicity) with up to 8 infusions of a rituximab product, and 35 received up to 6 cycles of bendamustine and a rituximab product. The median age overall was 68 years (range: 32-90); 67% were male; 92% were white; and 88% had an ECOG performance status of 0 or 1.

In the CALQUENCE arm, serious adverse reactions occurred in 29% of patients. Serious adverse reactions in > 5% of patients who received CALQUENCE included lower respiratory tract infection (6%). Fatal adverse reactions within 30 days of the last dose of CALQUENCE occurred in 2.6% of patients, including from second primary malignancies and infection.

In recipients of CALQUENCE, permanent discontinuation due to an adverse reaction occurred in 10% of patients, most frequently due to second primary malignancies followed by infection. Adverse reactions led to dosage interruptions of CALQUENCE in 34% of patients, most often due to respiratory tract infections followed by neutropenia, and dose reduction in 3.9% of patients.

Selected adverse reactions are described in Table 7 and non-hematologic laboratory abnormalities are described in Table 8. These tables reflect exposure to CALQUENCE with median duration of 15.7 months with 94% of patients on treatment for greater than 6 months and 86% of patients on treatment for greater than 12 months. The median duration of exposure to idelalisib was 11.5 months with 72% of patients on treatment for greater than 6 months and 48% of patients on treatment for greater than 12 months. Eighty-three percent of patients completed 6 cycles of bendamustine and rituximab product.

**Table 7: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE in Patients with CLL (ASCEND)**

| Body System Adverse Reaction* | CALQUENCE N=154 | | Idelalisib plus Rituximab Product N=118 | | Bendamustine plus Rituximab Product N=35 | |
|---|---|---|---|---|---|---|
| | All Grades (%) | Grade ≥ 3 (%) | All Grades (%) | Grade ≥ 3 (%) | All Grades (%) | Grade ≥ 3 (%) |
| **Infections** | | | | | | |
| Infection† | 56 | 15‡ | 65 | 28‡ | 49 | 11 |
| Upper respiratory tract infection[a] | 29 | 1.9 | 26 | 3.4 | 17 | 2.9 |
| Lower respiratory tract infection[b] | 23 | 6 | 26 | 15 | 14 | 6 |
| **Blood and lymphatic system disorders** § | | | | | | |
| Neutropenia[c] | 48 | 23 | 79 | 53 | 80 | 40 |
| Anemia[d] | 47 | 15 | 45 | 8 | 57 | 17 |
| Thrombocytopenia[e] | 33 | 6 | 41 | 13 | 54 | 6 |
| Lymphocytosis[f] | 26 | 19 | 23 | 18 | 2.9 | 2.9 |
| **Nervous system disorders** | | | | | | |
| Headache | 22 | 0.6 | 6 | 0 | 0 | 0 |
| **Gastrointestinal disorders** | | | | | | |
| Diarrhea[g] | 18 | 1.3 | 49 | 25 | 14 | 0 |
| **Vascular disorders** | | | | | | |
| Hemorrhage[h] | 16 | 1.3 | 5 | 1.7 | 6 | 2.9 |
| **General disorders** | | | | | | |
| Fatigue[i] | 15 | 1.9 | 13 | 0.8 | 31 | 6 |
| **Musculoskeletal and connective tissue disorders** | | | | | | |
| Musculoskeletal pain[j] | 15 | 1.3 | 15 | 1.7 | 2.9 | 0 |

*Per NCI CTCAE version 4.03
† Includes any adverse reactions involving infection or febrile neutropenia
‡ Includes 1 fatal case in the CALQUENCE monotherapy arm and 1 fatal case in the Idelalisib plus Rituximab arm
§ Derived from adverse reaction and laboratory data
[a] Upper respiratory tract infection, rhinitis and nasopharyngitis
[b] Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection.
[c] Includes neutropenia, neutrophil count decreased, and related laboratory data
[d] Includes anemia, red blood cell decreased, and related laboratory data
[e] Includes thrombocytopenia, platelet count decreased, and related laboratory data
[f] Includes lymphocytosis, lymphocyte count increased and related laboratory data
[g] Includes colitis, diarrhea, and enterocolitis
[h] Includes hemorrhage, hematoma, hemoptysis, hematuria, menorrhagia, hemarthrosis, and epistaxis
[i] Includes asthenia, fatigue, and lethargy
[j] Includes back pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, pain in extremity, myalgia, spinal pain and bone pain

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE included:

- *Skin and subcutaneous disorders*: bruising (10%), rash (9%)
- *Neoplasms*: second primary malignancy (12%), non-melanoma skin cancer (6%)
- *Musculoskeletal and connective tissue disorders*: arthralgia (8%)
- *Cardiac disorders*: atrial fibrillation or flutter (5%), hypertension (3.2%)
- *Infection*: herpesvirus infection (4.5%)

**Table 8: Select Non-Hematologic Laboratory Abnormalities (≥ 10% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ASCEND)**

| Laboratory Abnormality [a] | CALQUENCE N=154 | | Idelalisib plus Rituximab Product N=118 | | Bendamustine plus Rituximab Product N=35 | |
|---|---|---|---|---|---|---|
| | All Grades (%) | Grade ≥ 3 (%) | All Grades (%) | Grade ≥ 3 (%) | All Grades (%) | Grade ≥ 3 (%) |
| Uric acid increase | 15 | 15 | 11 | 11 | 23 | 23 |
| ALT increase | 15 | 1.9 | 59 | 23 | 26 | 2.9 |
| AST increase | 13 | 0.6 | 48 | 13 | 31 | 2.9 |
| Bilirubin increase | 13 | 1.3 | 16 | 1.7 | 26 | 11 |

Per NCI CTCAE version 5
[a] Excludes electrolytes

Increases in creatinine to 1.5 to 3 times ULN occurred in 1.3% of patients who received CALQUENCE.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

Risk Summary

Based on findings in animals, CALQUENCE may cause fetal harm and dystocia when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of acalabrutinib to animals during organogenesis resulted in dystocia in rats and reduced fetal growth in rabbits at maternal exposures (AUC) 2 times exposures in patients at the recommended dose of 100 mg approximately every 12 hours (*see Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

*Animal Data*

In a combined fertility and embryo-fetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day [GD] 17. No effects on embryo-fetal development and survival were observed. The AUC at 200 mg/kg/day in pregnant rats was approximately 9-times the AUC in patients at the recommended dose of 100 mg approximately every 12 hours. The presence of acalabrutinib and its active metabolite were confirmed in fetal rat plasma.

In an embryo-fetal development study in rabbits, pregnant animals were administered acalabrutinib orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Administration of acalabrutinib at doses ≥ 100 mg/kg/day produced maternal toxicity and 100 mg/kg/day resulted in decreased fetal body weights and delayed skeletal ossification. The AUC at 100 mg/kg/day in pregnant rabbits was approximately 2-times the AUC in patients at 100 mg approximately every 12 hours.

In a pre- and postnatal development study in rats, acalabrutinib was administered orally to pregnant animals during organogenesis, parturition and lactation, at doses of 50, 100, and 150 mg/kg/day. Dystocia (prolonged or difficult labor) and mortality of offspring were observed at doses ≥ 100 mg/kg/day. The AUC at 100 mg/kg/day in pregnant rats was approximately 2-times the AUC in patients at 100 mg approximately every 12 hours. Underdeveloped renal papilla was also observed in F1 generation offspring at 150 mg/kg/day with an AUC approximately 5-times the AUC in patients at 100 mg approximately every 12 hours.

### Lactation

Risk Summary

No data are available regarding the presence of acalabrutinib or its active metabolite in human milk, its effects on the breastfed child, or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Due to the potential for adverse reactions in a breastfed child from CALQUENCE, advise lactating women not to breast-feed while taking CALQUENCE and for at least 2 weeks after the final dose.

### Females and Males of Reproductive Potential

Pregnancy

Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy.

Contraception

*Females*

CALQUENCE may cause embryo-fetal harm and dystocia when administered to pregnant women *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for at least 1 week following the last dose of CALQUENCE. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

### Pediatric Use

The safety and efficacy of CALQUENCE in pediatric patients have not been established.

### Geriatric Use

Of the 929 patients with CLL or MCL in clinical trials of CALQUENCE, 68% were 65 years of age or older, and 24% were 75 years of age or older. Among patients 65 years of age or older, 59% had Grade 3 or higher adverse reactions and 39% had serious adverse reactions. Among patients younger than age 65, 45% had Grade 3 or higher adverse reactions and 25% had serious adverse reactions. No clinically relevant differences in efficacy were observed between patients ≥ 65 years and younger.

### Hepatic Impairment

Avoid administration of CALQUENCE in patients with severe hepatic impairment. The safety of CALQUENCE has not been evaluated in patients with moderate or severe hepatic impairment *[see Recommended Dosage for Hepatic Impairment (2.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Distributed by:
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11/19 US-34117 11/19

# LEADING A NEW ERA IN BTK INHIBITION

CALQUENCE®
(acalabrutinib) 100 mg capsules

## MORE PATIENTS START WITH CALQUENCE THAN ANY OTHER BTKi IN 1L CLL*[1]

SCAN HERE TO DISCOVER MORE

*Based on IMS claims data as of 2/2022.
1L=first-line; BTKi=Bruton tyrosine kinase inhibitor; CLL=chronic lymphocytic leukemia.

**Indication and Usage**
CALQUENCE is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

**Select Safety Information**
Serious adverse events, including fatal events, have occurred with CALQUENCE, including serious and opportunistic infections, hemorrhage, cytopenias, second primary malignancies, and atrial fibrillation and flutter. The most common adverse reactions (≥ 30%) of any grade in patients with CLL were anemia, neutropenia, thrombocytopenia, headache, upper respiratory tract infection, and diarrhea.

**Please see Brief Summary of full Prescribing Information on adjacent pages.**

*You are encouraged to report negative side effects of prescription drugs to the FDA.*
*Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.*

**Reference: 1.** Data on File, REF-63120. AstraZeneca Pharmaceuticals LP.

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