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

February 2024 Volume 22, Issue 1, Supplement 2

A SPECIAL MEETING REVIEW EDITION

Highlights in Chronic Lymphocytic Leukemia From the 65th ASH Annual Meeting and Exposition

A Review of Selected Presentations From ASH 2023 • December 9-12, 2023 • San Diego, California

Special Reporting on:

- Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of ELEVATE-TN
- Relapse After First-Line Fixed Duration Ibrutinib + Venetoclax: High Response Rates to Ibrutinib Retreatment and Absence of BTK Mutations in Patients With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) With Up to 5 Years of Follow-up in the Phase 2 CAPTIVATE Study
- Ibrutinib Plus Venetoclax With MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI FLAIR Study
- First-Line Venetoclax Combinations in Fit Patients With CLL: 4-Year Follow-up and NGS-Based MRD Analysis From the Phase 3 GAIA/CLL13 Trial
- Extended Follow-up of ALPINE Randomized Phase 3 Study Confirms Sustained Superior Progression-Free Survival of Zanubrutinib Versus Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL)
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PLUS Meeting Abstract Summaries

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Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of ELEVATE-TN

Inhibition of Bruton tyrosine kinase (BTK) in patients with chronic lymphocytic leukemia (CLL) has revolutionized the treatment of this disease, yielding significant improvements in efficacy outcomes vs traditional therapy.[1,2] Acalabrutinib is a BTK inhibitor that is approved for the treatment of adult patients with CLL/small lymphocytic lymphoma (SLL).[3] The international, open-label, phase 3 ELEVATE-TN trial evaluated acalabrutinib, with or without obinutuzumab, vs chlorambucil plus obinutuzumab in patients with treatment-naive CLL.[4-7] The study included patients aged 65 years or older, and patients between 18 and 65 years of age were eligible if they had a creatinine clearance rate of 30 to 69 mL/min and a Cumulative Illness Rating Score-Geriatric (CIRS-G) above 6. Patients with significant cardiovascular disease were excluded. Stratification factors included chromosome 17p deletion (del[17p]), Eastern Cooperative Oncology Group performance status, and geographic region. Patients were evenly randomized into the 3 treatment arms. Acalabrutinib (100 mg, daily) was administered until disease progression or unacceptable toxicity; obinutuzumab and chlorambucil were administered for 6 cycles. The primary endpoint was progression-free survival (PFS) with acalabrutinib plus obinutuzumab vs PFS with chlorambucil plus obinutuzumab, assessed by independent review. Patients in the chlorambucil-plus-obinutuzumab arm with disease progression were allowed to cross over into the acalabrutinib monotherapy arm.

The ELEVATE-TN study included 535 patients with a median age of 70 years (range, 41-91). Across the 3 arms, the proportions of patients with bulky disease ranged from 26% to 38%, the proportions with del(17p) ranged from 8.9% to 9.6%, and the proportions with an unmutated immunoglobulin heavy chain variable region (IGHV) ranged from 10.6% to 11.9%. *TP53* mutation was observed in 10.6% to 11.9% of patients. After a median follow-up of 73.3 to 74.6 months, approximately half of patients continued to receive acalabrutinib therapy. The relative dose intensity was 93.9%±11.8% in the acalabrutinib-plus-obinutuzumab arm and 95.7%±10.0% in the acalabrutinib monotherapy arm. At 72 months, the median PFS was 78% with acalabrutinib plus obinutuzumab, 62% with acalabrutinib monotherapy, and 17% with chlorambucil plus obinutuzumab

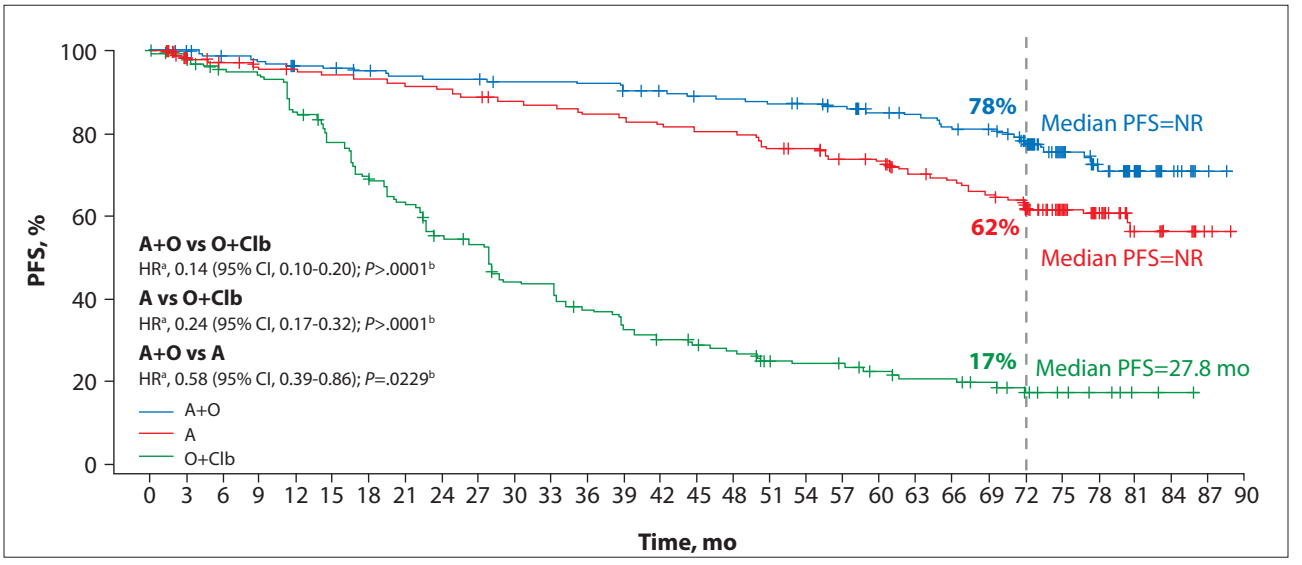

Figure 1. The PFS of acalabrutinib plus obinutuzumab vs the PFS of obinutuzumab plus chlorambucil for treatment-naive patients with CLL from the ELEVATE-TN study.

[a]HR based on stratified Cox proportional-hazards model.

[b]*P*-value based on stratified log-rank test.

A, acalabrutinib; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; HR, hazard ratio; mo, months; NR, not reached; O, obinutuzumab; PFS, progression-free survival.

Adapted from Sharman J et al. ASH abstract 636. *Blood*. 2023;142(suppl 1).[4]

(Figure 1). The trial continued to show a significant improvement in median PFS with acalabrutinib plus obinutuzumab vs chlorambucil plus obinutuzumab (HR, 0.14; 95% CI, 0.10-0.20; *P*<.0001). In a post hoc analysis, acalabrutinib plus obinutuzumab was also superior to acalabrutinib monotherapy in terms of PFS (HR, 0.58; 95% CI, 0.39-0.86; *P*=.0229), objective response rate (ORR; *P*=.022), and complete response (CR) rate (*P*=.022). Among all patients treated with acalabrutinib, achievement of a CR was associated with a longer PFS (*P*<.0001). Among patients with unmutated IGHV, acalabrutinib plus obinutuzumab yielded a superior median PFS vs chlorambucil plus obinutuzumab (HR, 0.08; 95% CI, 0.05-0.12; *P*<.0001), and acalabrutinib monotherapy was superior to chlorambucil plus obinutuzumab (HR, 0.12; 95% CI, 0.08-0.18; *P*<.0001); however, the difference between acalabrutinib with or without obinutuzumab was not significant (*P*=.2586). Among patients with del(17p) or *TP53* mutation, no differences in outcome were observed with the 3 treatment regimens. However, among patients lacking del(17p) or mutated *TP53*, a benefit was observed with obinutuzumab plus acalabrutinib vs acalabrutinib monotherapy. At 72 months, the median overall survival (OS) was 87% with acalabrutinib plus obinutuzumab, 80% with chlorambucil plus obinutuzumab (*P*=.0349), and 79% with acalabrutinib monotherapy.

Rates of adverse events (AEs) of clinical interest were similar to those previously reported and were similar in the 2 acalabrutinib-containing arms. Rates of cardiac-related AEs remained low. Atrial fibrillation of any grade was reported in 7% to 9% of patients, major bleeding of any grade was observed in 6% to 9% of patients, and hypertension was observed in 11% of patients.

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Relapse After First-Line Fixed Duration Ibrutinib + Venetoclax: High Response Rates to Ibrutinib Retreatment and Absence of BTK Mutations in Patients With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) With Up to 5 Years of Follow-up in the Phase 2 CAPTIVATE Study

Ibrutinib is a BTK inhibitor that is approved for the treatment of adult patients with CLL/SLL.[1] Venetoclax is an oral inhibitor of B-cell leukemia/lymphoma 2 (BCL2) that is also approved for the treatment of CLL/SLL.[2] The international phase 2 CAPTIVATE study evaluated ibrutinib plus venetoclax as first-line therapy in patients with CLL/SLL.[3-5] All patients received initial therapy consisting of 3 cycles of ibrutinib followed by 12 cycles of ibrutinib plus venetoclax. Patients enrolled in the fixed-dose (FD) cohort received no further therapy. After the initial 15 cycles of study therapy, patients in the measurable residual disease (MRD) cohort were randomized into 4 arms. Those with confirmed undetectable MRD were randomized to receive placebo vs ibrutinib monotherapy, while patients without confirmed undetectable MRD were randomized to receive ibrutinib vs ibrutinib plus venetoclax. A 5-year efficacy and safety analysis included 159 patients from the FD cohort and 43 patients from the MRD placebo arm. Among these 202 patients, 53 had experienced disease progression, which occurred more than 2 years after the completion of study therapy in 33 patients (62%). Of the 53 patients, 49 had progressive CLL and 4 had Richter transformation. A comparison of baseline characteristics in the 49 patients with CLL relapse vs baseline characteristics in the 149 patients without disease progression suggested that patients whose disease progressed were more likely to have del(17p)/mutated *TP53* (22% vs 11%), del(11q) (27% vs 15%), or unmutated IGHV (76% vs 52%).

Bone marrow and/or peripheral blood samples were available at disease progression from 40 patients who received FD therapy. None of these patients had mutations in the *BTK* or *PLCG2* gene, which can confer resistance to ibrutinib. One patient had an

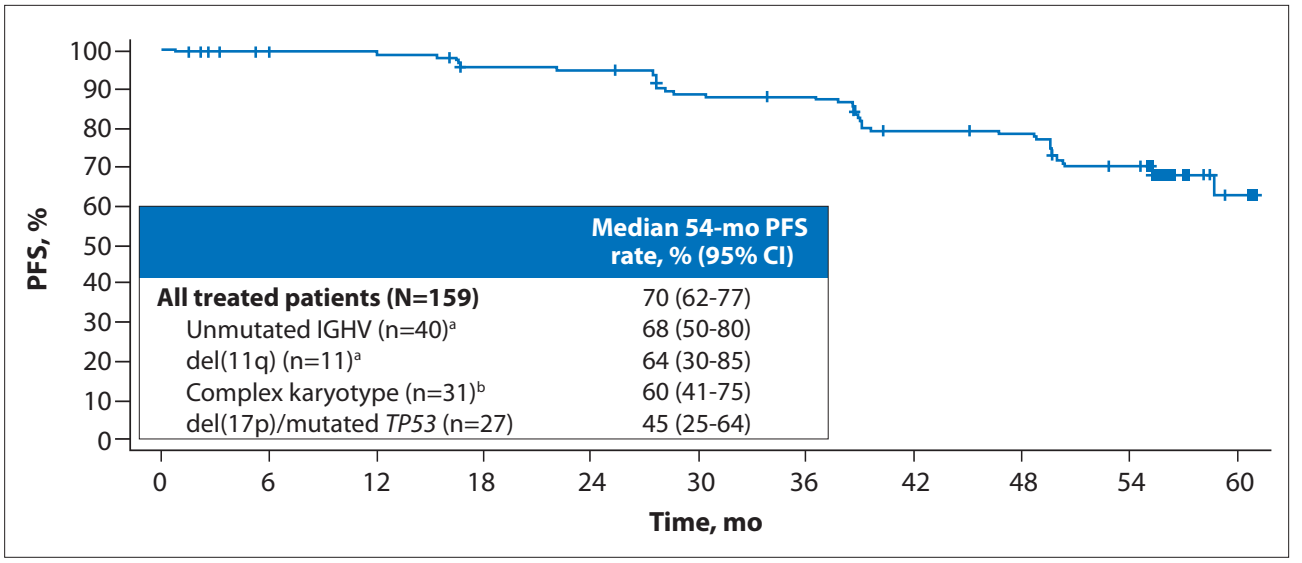

Figure 2. Overall median PFS of ibrutinib plus venetoclax in patients with CLL/SLL from the fixed duration cohort of the phase 2 CAPTIVATE study.

[a]Excluding patients with del(17p)/mutated *TP53* or complex karyotype.

[b]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.

CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain variable; mo, months; PFS, progression-free survival; SLL, small lymphocytic lymphoma.

Adapted from Ghia P et al. ASH abstract 633. *Blood*. 2023;142(suppl 1).[3]

unusual A113G mutation in *BCL2*, which did not appear to attenuate the response to venetoclax. Among the 202 patients in the FD cohort, the median time to next treatment was not reached. The estimated 4.5-year rate of freedom from next line of treatment was 82% (95% CI, 76%-87%). In the 28 patients who experienced disease progression, ibrutinib therapy was reinitiated (22 with ibrutinib alone and 6 with ibrutinib plus venetoclax), and in these 28 patients, the median time from the end of treatment to disease progression was 2.1 years (range, 0.2-4.3). After a median 17 months (range, 0-45) on retreatment with ibrutinib monotherapy, the ORR was 86%, including 5% CRs. After a median 14 months (range, 5-15) of retreatment with ibrutinib plus venetoclax, the ORR was 83%, including 33% CRs.

In the FD cohort, after 5 years of follow-up, the median PFS was not reached. The 54-month PFS rate was 70% (95% CI, 62%-77%). On the basis of genetic or chromosomal abnormalities, the median PFS rate at 54 months was lowest among the subgroup of patients with del(17p)/*TP53* mutation (45%; 95% CI, 25%-64%) and highest among the subgroup of patients with unmutated IGHV (68%; 95% CI, 50%-80%) (Figure 2). The median OS rate was 97% (95% CI, 93%-99%), the ORR was 96%, and the rate of CR/incomplete CR (CRi) was 58%. The combination of ibrutinib plus venetoclax continued to show a manageable safety profile after up to

ABSTRACT SUMMARY BELLWAVE-010: Phase 3, Open-Label, Randomized Study of Nemtabrutinib Plus Venetoclax Versus Venetoclax Plus Rituximab in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Following at Least One Prior Therapy

The open-label, active-controlled, phase 3 BELLWAVE study is evaluating nemtabrutinib plus venetoclax vs rituximab plus venetoclax in patients with previously treated CLL/SLL with and without C481 mutation (Abstract 3287). Part 1 will enroll 30 patients to determine the optimal dose of nemtabrutinib. Patients in Part 2 will be evenly randomized to receive either nemtabrutinib or rituximab, combined with venetoclax. Stratification factors include *BTK* C481 mutation status, risk factors, and geographic region. Patients in the experimental arm will receive nemtabrutinib alone at the recommended dose for 28 days, followed by nemtabrutinib plus venetoclax. Rituximab and venetoclax will be administered according to standard practice. The primary endpoint for Part 2 is the blinded, independently assessed PFS according to iwCLL 2018 criteria. Other endpoints will evaluate efficacy, safety, and quality of life.

5 years of follow-up in this population of patients with CLL.

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Ibrutinib Plus Venetoclax With MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI FLAIR Study

Key studies in CLL over the last decade have compared the safety and efficacy of BTK inhibitors, alone or combined with other agents, with the safety and efficacy of the combination of fludarabine, cyclophosphamide, and rituximab (FCR). The multicenter, open-label, parallel group, phase 3 FLAIR trial investigated ibrutinib monotherapy, ibrutinib plus rituximab, and ibrutinib plus venetoclax vs FCR in patients with CLL. Results from a preplanned interim analysis have been published.[1] For the third comparison of the FLAIR study, 523 patients were enrolled at 96 treatment centers in the United Kingdom from July 2017 to March 2021.[2,3] Patients were required to have previously untreated CLL requiring therapy according to criteria from the International Workshop on CLL (iwCLL) and to be no older than 75 years.[4] Patients with any prior Richter transformation or more than 20% *TP53* deletion by fluorescence in situ hybridization were excluded, as were patients with symptomatic cardiac failure or angina. Enrolled patients were evenly randomized to receive ibrutinib (420 mg, daily) plus venetoclax (escalated to 400 mg, daily) vs FCR. The primary endpoint was PFS.

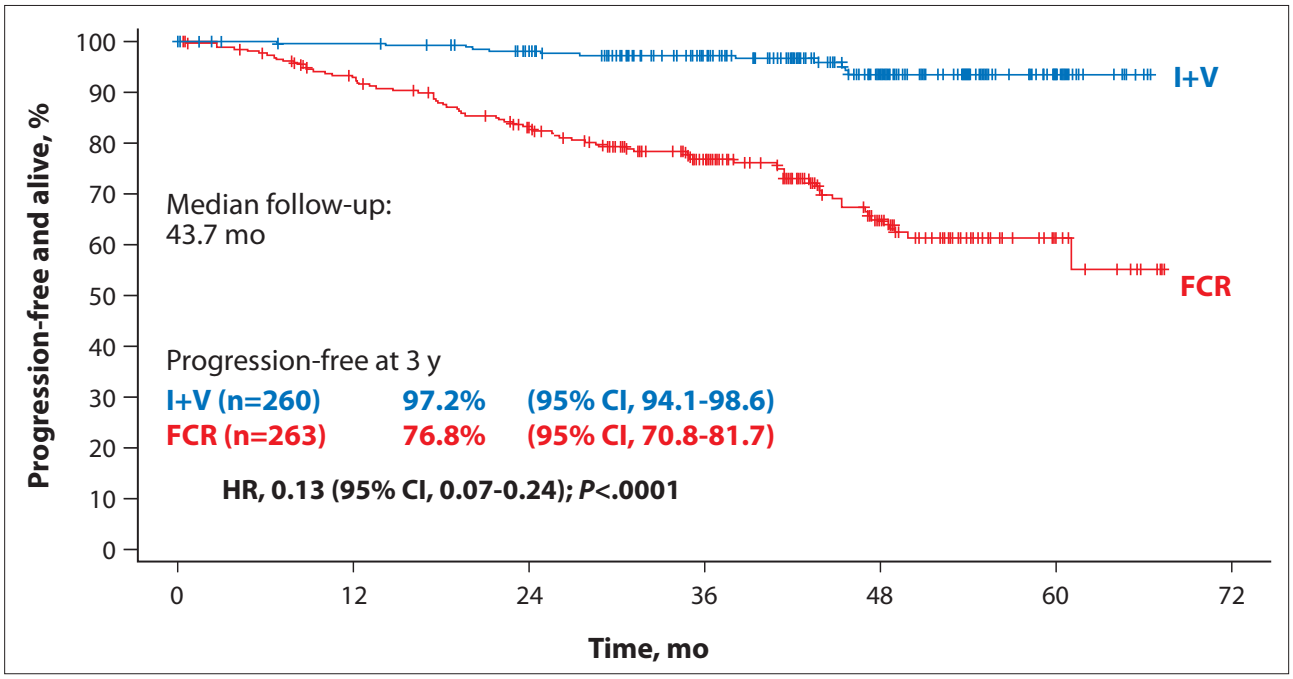

Figure 3. The PFS for fludarabine, cyclophosphamide, and rituximab vs the PFS for ibrutinib plus venetoclax in patients with previously untreated CLL from the phase 3 FLAIR study.
CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio; I, ibrutinib; mo, months; PFS, progression-free survival; V, venetoclax; y, years.
Adapted from Hillmen P et al. ASH abstract 631. *Blood*. 2023;142(suppl 1).[2]

In the FLAIR trial, the administration of FCR was limited to 6 cycles, which is the accepted limit because of cumulative toxicity with the regimen. Critically in this trial, in an effort to optimize response rates with the ibrutinib combination, the total number of cycles of ibrutinib plus venetoclax was variable, depending on patient response. Patients were regularly monitored for MRD after the initiation of ibrutinib plus venetoclax. Once they achieved undetectable MRD, they continued the combination for twice as long as it took for them to achieve undetectable MRD. Therefore, patients who had undetectable MRD sooner received a shorter overall duration of therapy with ibrutinib plus venetoclax. Duration of therapy was guided by undetectable MRD assessed by flow cytometry analysis of peripheral blood and bone marrow samples.

The 523 patients included in the analysis had a median age of 62 years, and 42% had Binet stage C disease. The median duration of CLL disease before randomization was 36 months, and 48% of patients had B symptoms. Half of the patients had unmutated IGHV, and the most common genetic abnormality was del(13q) (36%), followed by del(11q) (18%). At 9 months, the ORR was 87% with ibrutinib plus venetoclax vs 76% with FCR (P<.05), with CR rates of 59% vs 49% (P<.05), respectively. Per the prespecified algorithm, 50% of patients stopped ibrutinib-plus-venetoclax therapy at 27 months, 63% stopped at 39 months, and 73% stopped at 51 months. After a median follow-up of 43.7 months, the trial met its primary endpoint, demonstrating a median 3-year PFS of 97.2% with ibrutinib plus venetoclax vs 76.8% with FCR (HR, 0.13; 95% CI, 0.07-0.24; P<.0001) (Figure 3). The trial also demonstrated an OS benefit with the ibrutinib combination vs FCR (HR, 0.31; 95% CI, 0.15-0.67; P<.005). Notably, the improvement in survival endpoints was evident in the subpopulation of patients with unmutated IGHV per median PFS (HR, 0.07; 95% CI, 0.02-0.29; P<.001) and median OS (HR, 0.23; 95% CI, 0.06-0.81; P=.022). However, the 2 treatments yielded similar rates of PFS and OS in patients with mutated IGHV (P>.05). Treatment with ibrutinib plus venetoclax was generally well tolerated, with no new safety signals.

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First-Line Venetoclax Combinations in Fit Patients With CLL: 4-Year Follow-up and NGS-Based MRD Analysis From the Phase 3 GAIA/CLL13 Trial

The open-label, phase 3 GAIA/CLL13 trial evaluated 3 different venetoclax-based regimens vs chemoimmunotherapy in fit patients with previously untreated CLL.[1,2] Patients with *TP53* mutation were not allowed. Eligible patients were evenly randomized into the 4 treatment arms. Patients in the experimental arms received either rituximab plus venetoclax (RV) for 12 months, obinutuzumab plus venetoclax (OV) for 12 months, or OV plus ibrutinib (OVI) for 12 to 36 months. In the control arm, patients aged 65 years or younger received FCR, and older patients received bendamustine plus rituximab (BR). Treatment in the OVI arm was guided by MRD; patients who failed to achieve undetectable MRD by month 15 were allowed to continue ibrutinib monotherapy for up to a total of 36 cycles. The trial had 2 coprimary endpoints: the rate of undetectable MRD at month 15 and the PFS.

The GAIA/CLL13 study enrolled 926 patients with a median age of 61 years (range, 27-84). The median CIRS-G score was 2 (range, 0-7). Of the 926 patients, 56% had unmutated IGHV and 17% had complex karyotype. The median observation time was 50.7 months, and the median observation time after the end of treatment was 40.7 months. The highest rate of early discontinuation of study therapy was in the chemoimmunotherapy arm (14.8%), followed by the OVI arm (11.7%), the RV arm (4.6%), and the OV arm (3.9%). The median 4-year PFS rate was significantly higher with OVI than with chemoimmunotherapy (85.5% vs 62.0%; HR, 0.30; 97.5% CI, 0.19-0.47; P<.001) (Figure 4). Per the median 4-year PFS, the OVI regimen was superior to RV (P<.001), OV was superior to chemoimmunotherapy (P<.001), and OV was superior to RV (P=.001). All of the venetoclax regimens were superior to chemoimmunotherapy in terms of median PFS in patients with unmutated IGHV (P<.05). Among patients with mutated IGHV, the median PFS rate was significantly higher with OVI vs chemoimmuno-

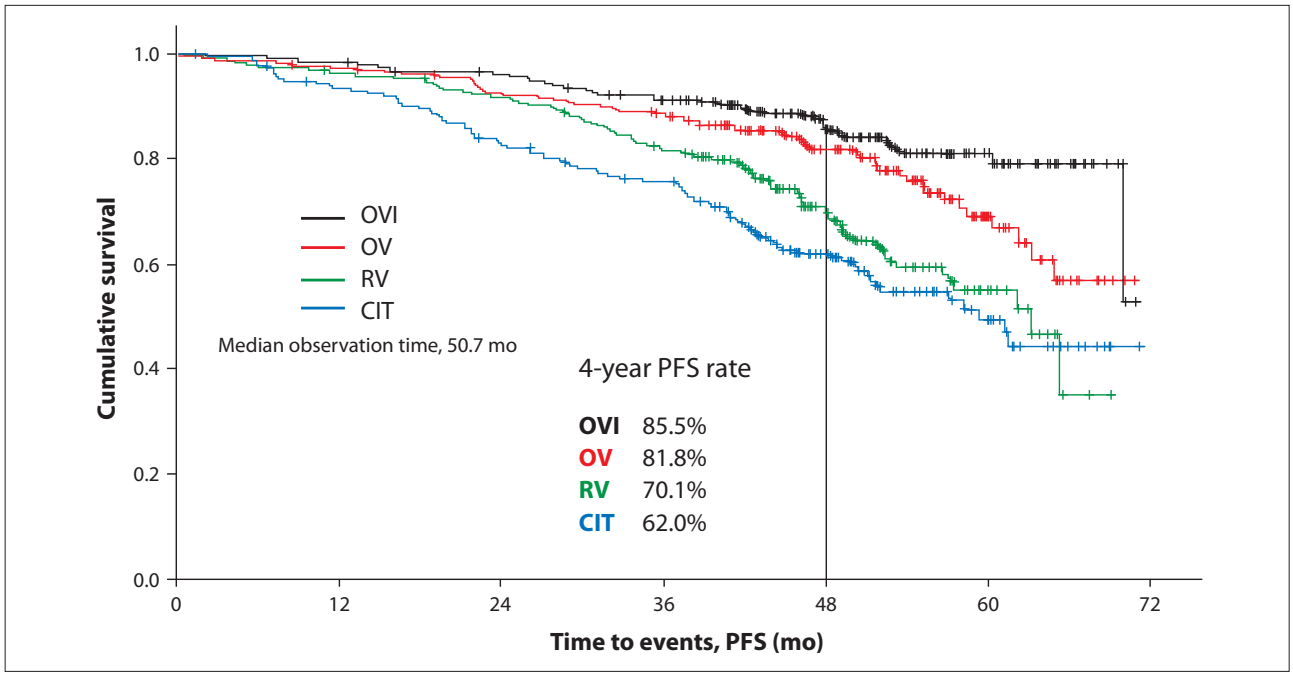

Figure 4. PFS according to treatment arm for patients with CLL from the phase 3 GAIA/CLL13 trial.
CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; OVI, obinutuzumab/venetoclax plus ibrutinib; OV, obinutuzumab/venetoclax; mo, months; PFS, progression-free survival; RV; rituximab/venetoclax.
Adapted from Fürstenau M et al. ASH abstract 635. *Blood*. 2023;142(suppl 1).[2]

therapy, with OVI vs RV, and with OV vs RV (P<.05). Analysis of OS did not reveal any significant differences among the treatment arms.

At month 15, the rate of undetectable MRD was highest in the OVI arm (66.2%), followed by the OV arm (60.3%), the RV arm (23.6%), and the control arm (22.7%). PFS curves were generated according to the MRD level at month 15 in each arm. This analysis showed a positive correlation between increasing depth of MRD at month 15 and prolonged PFS. Another analysis that investigated the relationship between the depth of MRD at 15 months and iwCLL response in patients pooled from the OV and OVI arms suggested that achievement of MRD of less than 10^{-6} closely resembles a CR.[3] The rate of grade 3 to 5 infection was highest with chemoimmunotherapy (33 events per 1000 patient-months [E1000]), followed by OVI (20 E1000), OV (14 E1000), and RV (10 E1000). The rate of cardiac AEs was highest with OVI (15 E1000), followed by chemoimmunotherapy (12 E1000), OV (7 E1000), and RV (7 E1000).

ABSTRACT SUMMARY Broad Superiority of Zanubrutinib (Zanu) Over Bendamustine + Rituximab (BR) Across Multiple High-Risk Factors: Biomarker Subgroup Analysis in the Phase 3 SEQUOIA Study in Patients With Treatment-Naive (TN) Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) Without del(17p)

The multicenter, open-label, phase 3 SEQUOIA study evaluated zanubrutinib monotherapy vs BR in patients with treatment-naive CLL/SLL who were elderly or had comorbidities (Abstract 1902; Tam CS et al. *Lancet Oncol*. 23;8:1031). In the first cohort, 479 patients without del(17p) were evenly randomized into the 2 treatment arms. Zanubrutinib elicited a significantly better median PFS vs BR among patients with del(11q) (P<.001), del(13q) (P<.001), trisomy 12 (P<.01), or complex karyotype (P<.01). The PFS benefit from ibrutinib plus venetoclax was similar among patients with and without del(11q) (P=.05). The PFS benefit with zanubrutinib vs BR was also observed among patients with unmutated IGHV (P<.0001) or mutated IGHV (P<.01).

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Extended Follow-up of ALPINE Randomized Phase 3 Study Confirms Sustained Superior Progression-Free Survival of Zanubrutinib Versus Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL)

Zanubrutinib is a highly selective BTK inhibitor.[1,2] Whereas ibrutinib and acalabrutinib have active metabolites, as well as off-target activity, zanubrutinib has reduced off-target activity, no active metabolite, and favorable pharmacokinetics.[3] The international phase 3 ALPINE trial evaluated zanubrutinib vs ibrutinib in patients with relapsed or refractory CLL/SLL.[4,5] Eligible patients had received at least 1 prior therapy for the CLL/SLL, had measurable lymphadenopathy, and required treatment according to the iwCLL criteria.[6] Patients who had received prior BTK inhibitor therapy were excluded. Stratification factors included age, refractory status, del(17p)/*TP53* mutation, and geographic region. Patients were evenly randomized to receive zanubrutinib (160 mg, twice daily) or ibrutinib (420 mg, once daily).

The ALPINE trial enrolled 652 patients with a median age of 67.5 years (range, 35-90). Patients had received a median 1 prior line of systemic therapy (range, 1-12). Genetic and chromosomal characteristics included del(17p)/*TP53* mutation (23%), unmutated IGHV (74%), and complex karyotype (19%). Bulky disease was noted in 45% of patients. After a median follow-up of 39 months, treatment was ongoing in 59% of patients in the zanubrutinib arm vs 47% in the ibrutinib arm. Zanubrutinib continued to show a superior PFS benefit compared with ibrutinib (3-year median PFS, 64.9% vs 54.8%; HR, 0.68; 95% CI, 0.53-0.86; *P*=.0011) (Figure 5). Zanubrutinib showed a favorable PFS benefit vs ibrutinib in most of the subgroups examined, which were based on age, prior lines of therapy, disease stage, and other factors. Notably, zanubrutinib yielded a superior median 3-year PFS among patients with del(17p)/*TP53* mutation (58.6% vs 41.3%; HR, 0.52; 95% CI, 0.33-0.83; *P*=.0047), and the zanubrutinib PFS benefit was observed across multiple sensitivity analyses. The ORR and rate of CR/CRi improved over time. With longer follow-up, the median 3-year OS was 82.5% with zanubrutinib vs 79.6% with ibrutinib, but the difference was not significant (*P*=.098).

The median duration of treatment was slightly longer in the zanubrutinib arm (38.3 vs 35.0 months). Grade 5 AEs occurred in 12% to 13% of patients in each arm. The rate of serious AEs was numerically higher in the ibrutinib arm (50.9% vs 59.0%), as were the rates of dose reduction (14.5% vs 18.2%), study treatment discontinuation (19.8% vs 26.2%), and hospitalization (46.3% vs 55.6%). The rate of dose interruption was 60.5% with zanubrutinib vs 62.0% with ibrutinib. In the zanubrutinib arm vs the ibrutinib arm, rates of any-grade AEs of special interest included hypertension (26.5% vs 24.7%), atrial fibrillation or flutter (6.8% vs 16.4%), and neutropenia (30.9% vs 29.0%),

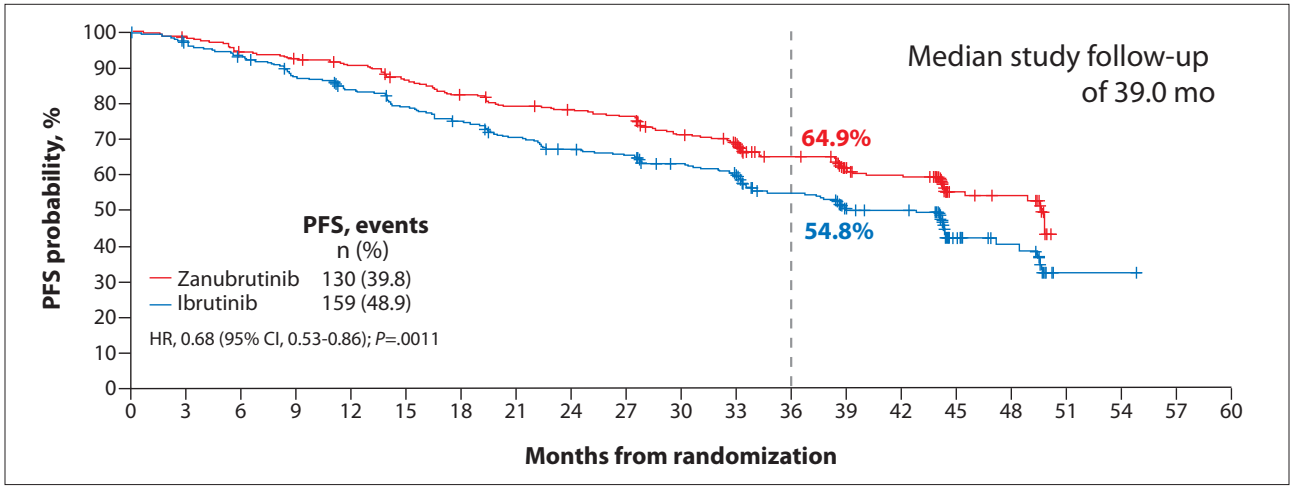

Figure 5. PFS for zanubrutinib vs ibruntinib in patients with R/R CLL/SLL at extended follow-up from the phase 3 ALPINE study.
CLL, chronic lymphocytic leukemia; mo, months; PFS, progression-free survival; R/R, relapsed or refractory; SLL, small lymphocytic lymphoma.
Adapted from Brown M et al. ASH abstract 202. *Blood*. 2023;142(suppl 1).[5]

respectively. Zanubrutinib continued to show a more favorable cardiac safety profile in comparison with ibrutinib, with cardiac AEs reported in 24.7% vs 34.6% of patients, respectively.

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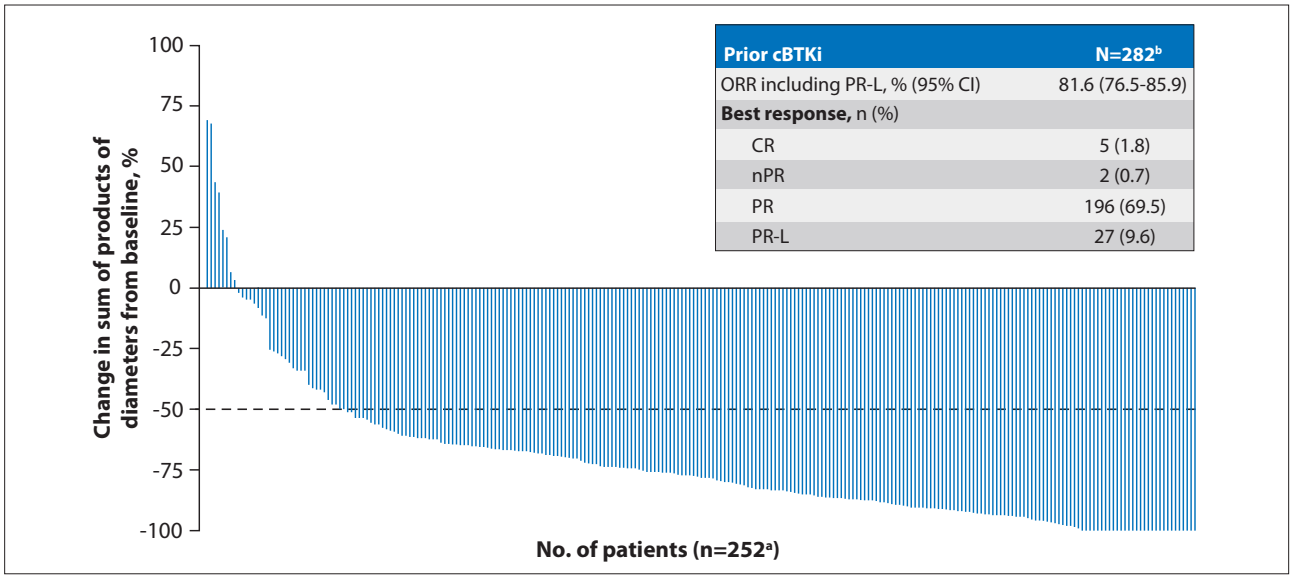
Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-up and Subgroup Analysis With/Without Prior BCL2i From the Phase 1/2 BRUIN Study

Pirtobrutinib is a selective, noncovalent BTK inhibitor that has shown promising efficacy and safety in early-stage clinical trials.[1-3] The drug inhibits both wild-type and C481-mutated *BTK* at a low concentration. Pharmacokinetic data suggest 96% BTK target inhibition and a half-life of approximately 20 hours. The noncovalent binding of pirtobrutinib appears to stabilize BTK in an inactive conformation, blocking both kinase-dependent and kinase-independent signaling. The multicenter phase 1/2 BRUIN study used dose escalation and a 3 + 3 expansion trial design to evaluate pirtobrutinib in patients with CLL/SLL and other B-cell malignancies.[4] Patients received pirtobrutinib at daily doses ranging from 25 to 300 mg. Intra-patient dose escalation was allowed, with cohort expansion permitted at dose levels that were considered safe. A key endpoint of the study was to determine the recommended phase 2 dose of pirtobrutinib in this patient setting, with additional safety, efficacy, and pharmacokinetic endpoints.

The BRUIN trial included 282 patients who had received prior covalent BTK inhibitor therapy, including 154 with prior BCL2 inhibitor exposure and 128 without. The 282



Prior cBTKi	N=282[b]
ORR including PR-L, % (95% CI)	81.6 (76.5-85.9)
Best response, n (%)	
CR	5 (1.8)
nPR	2 (0.7)
PR	196 (69.5)
PR-L	27 (9.6)

Figure 6. Pirtobrutinib efficacy in all patients with CLL/SLL who received prior cBTKi from the phase 1/2 BRUIN study.
[a]Data for 30 of 282 patients are not shown in the waterfall plot because of no measurable target lesions identified by CT at baseline, discontinuation before first response assessment, or lack of adequate imaging in follow-up.
[b]Post-cBTKi patients included a subgroup of 19 patients with 1 prior line of cBTKi-containing therapy and second-line therapy of pirtobrutinib, who had an ORR including PR-L of 89.5% (95% CI, 66.9-98.7).
cBTKi, covalent Bruton tyrosine kinase inhibitors; CLL, chronic lymphocytic leukemia, CR, complete response; CT, computed tomography; nPR, nodular partial response; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SLL, small lymphocytic lymphoma.
Adapted from Woyach et al. ASH abstract 235. *Blood*. 2023;142(suppl 1).[4]

patients had a median age of 69 years (range, 36-88), 43% had Rai stage III/IV disease, and 31% had bulky lymphadenopathy of at least 5 cm. *BTK* C481 mutation was noted in 39% of patients. High-risk molecular characteristics included unmutated IGHV (86%), del(17p)/*TP53* mutation (48%), complex karyotype (45%), and del(11q) (23%). Among the 282 patients with prior exposure to a covalent BTK inhibitor, the ORR was 81.6% (95% CI, 76.5%-85.9%) (Figure 6). Among patients without prior BCL2 inhibitor exposure, the ORR was 83.1% (95% CI, 76.2%-88.7%), and among those with prior BCL2 inhibitor exposure, the ORR was 79.7% (95% CI, 71.7%-86.3%). Pirtobrutinib therapy generally yielded consistent ORRs in subgroups based on age, Rai disease stage, performance status, and other factors.

Among the 282 patients with CLL/SLL in this analysis, the median PFS was 19.4 months (95% CI, 16.6-22.1) after a median follow-up of 27.5 months, and the 2-year PFS rate was 38.6%. Among patients without prior exposure to a BCL2 inhibitor, the median PFS was 23.0 months (95% CI, 19.6-28.4), and among those with prior exposure, the median PFS was 15.9 months (95% CI, 13.6-17.5). Among the 282 patients with prior exposure to covalent BTK inhibitor therapy, the 24-month OS was 73.2%, with the median OS not reached. Pirtobrutinib monotherapy was associated with a manageable safety profile. The most common treatment-emergent AEs of any grade were fatigue (36.9%), neutropenia (34.4%), and diarrhea (28.4%). The most common treatment-related AEs of grade 3 or higher were neutropenia (15.2%), followed by 2 AEs of special interest: infection (4.3%) and hemorrhage (1.1%). On December 1, 2023, the US Food and Drug Administration granted accelerated approval to pirtobrutinib for adult patients with CLL/SLL who have received at least 2 prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor.

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Lisocabtagene Maraleucel (liso-cel) in R/R CLL/SLL: 24-Month Median Follow-up of TRANSCEND CLL 004

Chimeric antigen receptor (CAR) T-cell therapy represents a groundbreaking advance in the treatment of cancers of the blood and is being investigated in CLL/SLL.[1] Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed CAR T-cell therapy that was investigated in patients with CLL/SLL in the multicenter, single-arm, phase 1/2 TRANSCEND CLL 004 trial.[2-4] Eligible patients had relapsed or refractory disease and had previously failed or were ineligible for therapy with a BTK inhibitor. Depending on their CLL risk category, patients were required to have failed 2 or 3 prior lines of therapy. Bridging therapy was allowed. Lymphodepletion was accomplished with fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) for 3 days. Liso-cel was administered within 2 to 7 days after lymphodepletion. The study investigated 2 dose levels of liso-cel: 50 × 10^6 CAR T cells (DL1) and 100 × 10^6 CAR T cells (DL2). The primary endpoint was the CR/CRi rate at DL2 by independent review in a prespecified subset of patients who had failed prior therapy with a BTK inhibitor and venetoclax.[5]

The entire study population consisted of 118 patients with a median age of 65 years (range, 49-82). Patients had received a median 5 prior lines of therapy (range, 2-14). Bulky lymph nodes were noted in 45% of the patients, and 83% had high-risk cytogenetics. Prior BTK inhibitor and venetoclax therapy had been given to 81% of the patients, and 76% of them received bridging therapy. In the primary efficacy population of 50 patients, the CR/CRi rate was 20% (95% CI, 10%-34%) on the basis of iwCLL 2018 criteria, so that the primary endpoint was met (Table). The ORR was 44% (95% CI, 30%-59%), and the rate of undetectable MRD in the blood was 64% (95% CI, 49%-77%). The median duration of response was 35.3 months (95% CI, 12.4 months to not reached). The median PFS was 11.9 months (95% CI, 5.7-26.2), and among the 22 patients who exhibited a response, the median PFS was 38.1 months (95% CI, 13.4 months to not reached). The median OS for the 50 primary efficacy patients was 30.3 months (95% CI, 15.0 months to not reached).

No new safety signals arose. In the entire study population of 118 patients, the most common treatment-emergent AEs of any grade were cytokine release syndrome (85%, with no grade 4 or 5 events), anemia (67%), and neutropenia (62%). The most common treatment-emergent AEs of grade 3 or higher were cytopenias, including neutropenia (60%), thrombocytopenia (42%), and leukopenia (26%). Neurologic events were observed at grade 3 in 18% and grade 4 in 1% of patients. Death owing to treatment-emergent AEs that were considered unrelated to

Table. Lisocabtagene Maraleucel Efficacy Outcomes for Patients With R/R CLL/SLL From the TRANSCEND CLL 004 Study.

	Full Study Population at DL2 (N=88)	BTKi Progression/Venetoclax Failure Subset at DL2 (n=50)
Primary endpoint: IRC-assessed CR/CRi rate per iwCLL 2018, n (%) [95% CI]	17 (19) [12-29]	10 (20) [10-34]
Key secondary endpoints:		
IRC-assessed ORR, n (%) [95% CI]	42 (48) [37-59]	22 (44) [30-59]
uMRD rate in blood, n (%) [95% CI]	58 (66) [55-76]	32 (64) [49-77]
Exploratory endpoint: uMRD rate in marrow, n (%) [95% CI]	53 (60) [49-71]	30 (60) [45-74]
Other secondary endpoints		
Best overall response, n (%)		
CR/CRi	17 (19)	10 (20)
PR/nPR	25 (28)	12 (24)
SD	34 (39)	21 (42)
PD	6 (7)	4 (8)
Not evaluable	6 (7)	3 (6)
Median time to first response, mo (range)	1.3 (0.8-17.4)	1.1 (0.8-17.4)
Median time to first CR/CRi, mo (range)	5.5 (0.8-18.0)	2.1 (0.8-18.0)

BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete marrow recovery; DL2, dose level 2; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; mo, months; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed or refractory; SD, stable disease; SLL, small lymphocytic lymphoma; uMRD, undetectable minimal residual disease.
Adapted from Siddiqi et al. ASH abstract 330. *Blood*. 2023;142(suppl 1).[2]

study treatment occurred in 4 patients (3%). One patient (1%) died of macrophage-activation syndrome; this death was considered to be related to liso-cel treatment.

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Highlights in Chronic Lymphocytic Leukemia From the 2023 ASH Annual Meeting and Exposition: Commentary

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The 65th American Society of Hematology (ASH) Annual Meeting and Exposition took place in early December 2023 in San Diego, California. The event featured several presentations offering insight into the management of chronic lymphocytic leukemia (CLL), with data presented on a variety of drug combinations involving acalabrutinib, obinutuzumab, ibrutinib, venetoclax, zanubrutinib, pirtobrutinib, and lisocabtagene maraleucel.

Acalabrutinib/Obinutuzumab

The ELEVATE-TN trial compared frontline acalabrutinib with or without obinutuzumab vs chlorambucil plus obinutuzumab in patients with treatment-naive CLL.[1] This data set has been previously reported with shorter follow-up, but it is reassuring now to have the 6-year data presented at the 2023 ASH, which gives us more confidence in the durability of responses for both acalabrutinib-containing regimens.[2] One interesting aspect of this update is the continued improvement in progression-free survival (PFS) with the acalabrutinib/obinutuzumab combination vs acalabrutinib monotherapy in a post hoc analysis. This benefit appears to be absent for patients with

high-risk disease, specifically those with *TP53* aberrations. For patients with non–high-risk disease, it is worth considering offering the combination, although no overall survival (OS) advantage was found over acalabrutinib monotherapy. Therefore, it is not mandatory to choose the combination. In my practice, I have observed that most patients are still opting for Bruton tyrosine kinase (BTK) inhibitor monotherapy, as excellent results can be achieved without the inconvenience and additional toxicities associated with obinutuzumab.

Ibrutinib

Several studies at ASH evaluated the combination of ibrutinib plus venetoclax in patients with CLL. The CAPTIVATE trial is a multicenter, phase 2 study of ibrutinib plus venetoclax as first-line treatment for CLL/small lymphocytic lymphoma (SLL) in 2 cohorts: one guided by fixed duration and the other by minimal residual disease (MRD).[3] This most recent update focuses on the fixed duration cohort, now with 5 years of follow-up.[4] A notable aspect of the update is the thorough description of retreatment data with ibrutinib-based regimens in patients who previously received the ibrutinib-plus-venetoclax regimen and then went into remission, were off treatment, and later relapsed. The data presented in this abstract suggest that most patients respond well to retreatment. Although the durability of retreatment is still not fully understood, the initial results appear promising. This regimen is not approved by the US Food and Drug Administration (FDA) in the United States; however, it is listed in the National Comprehensive Cancer Network Guidelines, so that it is an option to consider for patients seeking an all-oral, time-limited regimen.[5] It is important to note that the patients in CAPTIVATE are younger, fitter patients with CLL, in whom the safety profile of this regimen looks better than it does in older patients and those with significant comorbidities.

The FLAIR trial is a large, phase 3 study running in the United Kingdom that features multiple different arms. What was presented at this year's ASH meeting and simultaneously published in *The New England Journal of Medicine* was the comparison of ibrutinib plus venetoclax vs fludarabine, cyclophosphamide, and rituximab (FCR).[6,7] This trial focused on a younger, fitter CLL population, and both regimens were anticipated to be effective. The data revealed an improvement in PFS with ibrutinib/venetoclax vs FCR, which was not surprising, especially because the patients could be on ibrutinib/venetoclax for several years, whereas FCR is only a 6-month therapy. What was interesting and surprising was the OS advantage of ibrutinib plus venetoclax over FCR, even though many patients whose disease progressed after FCR went on to receive targeted therapies. This speaks to the benefits of using targeted therapies for most patients with CLL, even those who are younger and fit. In other words, it matters what you start with. Another interesting aspect of the study was the use of MRD-guided duration of therapy with ibrutinib plus venetoclax. Patients received therapy for twice as long as it took to achieve undetectable MRD. This is a way to individualize the length of therapy to optimize outcomes. However, it is worth noting that this MRD-guided approach has not yet been directly compared with a fixed duration approach, and the superiority of one over the other in terms of outcomes is yet to be established. This study represents an encouraging first step in exploring the potential use of MRD-guided therapy to improve outcomes for patients.

Zanubrutinib

ALPINE provides another update on data that we saw published last year. This phase 3 trial compares ibrutinib with the more-selective BTK inhibitor zanubrutinib in relapsed/refractory (R/R) CLL.[8] With longer follow-up, a couple of interesting points have emerged. First, the PFS advantage of zanubrutinib over ibrutinib has been maintained with longer follow-up, suggesting that zanubrutinib may be a more efficacious BTK inhibitor than ibrutinib. Second, the safety profile of zanubrutinib continues to look promising with longer-term follow-up. No signal of late toxicities is associated with the drug, instilling confidence that patients can be treated with zanubrutinib and experience long-term remissions with good tolerability. Overall, it appears to be a helpful drug in clinical practice.

Venetoclax

CLL13 is a frontline study focusing on younger, fit patients with CLL who were treated with 1 of 4 different regimens: chemoimmunotherapy; venetoclax with rituximab; venetoclax with obinutuzumab; or a triplet therapy of ibrutinib, venetoclax, and obinutuzumab. Last year, data with 3 years of follow-up, including a report in *The New England Journal of Medicine*, were published.[9] At the 2023 ASH, 4 years of follow-up and detailed MRD-based analyses were shared.[10] The key takeaways from the update include that the obinutuzumab-containing arms continue to appear superior to the other arms of the study, in terms of both depth of MRD and PFS. The triplet therapy shows a slightly better performance than the doublet of venetoclax/obinutuzumab, but the difference is not dramatic. With 4 years of follow-up, my main conclusion is that venetoclax plus obinutuzumab remains the regimen to beat. So far, none of these other regimens has displaced it, and this study provides additional confidence that very durable responses can be achieved for younger, fit patients with CLL treated with venetoclax/obinutuzumab in the frontline setting.

Pirtobrutinib

Pirtobrutinib, a noncovalent BTK

inhibitor, was the focus of this presentation, and its timing was particularly noteworthy because it had received FDA approval for R/R CLL in early December, just before the presentation.[11] The data presented were from the BRUIN study and included a longer-term follow-up analysis with a median of 30 months of follow-up.[12] The patients were a very heavily pretreated group, with most having undergone several prior lines of therapy. A notable theme that has emerged with pirtobrutinib is its high level of activity even in patients with previous progression on a covalent BTK inhibitor and those with progression on both a covalent BTK inhibitor and the BCL2 inhibitor venetoclax. The response rate is quite high, and the durability is reasonably good in this population. It will be interesting to see how the use of this drug evolves over time. The presentation highlighted the promising future of pirtobrutinib, and additional studies exploring combinations of pirtobrutinib with venetoclax are now underway. Moreover, studies are investigating moving pirtobrutinib into earlier lines of therapy, including frontline therapy for CLL. This update was particularly timely, given that pirtobrutinib is now approved for patients with CLL and available to use in clinical practice.

Lisocabtagene Maraleucel

Lisocabtagene maraleucel (liso-cel) is a CD19-directed chimeric antigen receptor (CAR) T-cell therapy, and we had previously seen data published this past year.[13] Dr Siddiqi presented longer-term follow-up from that study of liso-cel monotherapy.[14] This involved a heavily pretreated group of patients with CLL, many of whom had disease refractory to both BTK inhibitors and venetoclax. Nonetheless, some durable responses were achieved. The complete response (CR) rate of 20% is modest, but among those patients who did achieve a CR, very few recurrences have been noted with 24 months of follow-up. This is encouraging, indicating that a subset of patients can derive very durable benefits from this product. It is important to note the risks of cytokine-release syndrome and neurologic side effects, especially in older patients with CLL. With this product currently under consideration for possible accelerated approval by the FDA, the TRANSCEND data set is valuable. If this product does become available, it will help guide us in understanding the likely outcomes for patients treated with an exciting new therapy.

Disclosures

Davids reports receiving grant support, paid to his institution, and consulting fees from Ascentage Pharma, AbbVie, AstraZeneca, Genentech, MEI Pharma, Novartis, and TG Therapeutics. He has received consulting fees from Adaptive Biotechnologies, BeiGene, BMS, Celgene, Eli Lilly, Genmab, Janssen, Merck, Nuvalent, Research To Practice, Secura Bio, and TG Therapeutics.

ABSTRACT SUMMARY Molecular Analysis at Relapse of Patients Treated on the Ibrutinib and Rituximab Arm of the National Multicentre Phase III FLAIR Study in Previously Untreated CLL Patients

In the FLAIR trial, 61 patients treated with ibrutinib plus rituximab had disease progression after a median follow-up of 44 months (Abstract 4636). At progression, *BTK* was the most frequently mutated gene. Among 57 samples sequenced at progression, 7 had hotspot *BTK* mutations that were not observed at baseline. In most cases (5/7), *BTK* mutation was reported after discontinuation of therapy at 72 months. One patient had a mutation in *PLCG2* at progression. Unmutated IGHV appeared to be a risk factor for acquiring *BTK* mutation with prolonged exposure to the BTK inhibitor.

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CALQUENCE® (acalabrutinib) tablets, 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 dosage 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 dosage 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 tablet whole with water. Advise patients not to chew, crush, dissolve, or cut the tablets. 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 tablets of CALQUENCE should not be taken to make up for a missed dose.

Recommended Dosage for Drug Interactions

Dosage 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 Dosage Modifications for Use with CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended CALQUENCE use
Inhibition	Strong CYP3A inhibitor	Avoid co-administration. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE. After discontinuation of strong CYP3A inhibitor for at least 24 hours, resume previous dosage of CALQUENCE.
	Moderate CYP3A inhibitor	Reduce the CALQUENCE 100 mg every 12 hours dosage to 100 mg once daily.
Induction	Strong CYP3A inducer	Avoid co-administration. If co-administration is unavoidable, increase CALQUENCE dosage to 200 mg approximately every 12 hours.

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

Table 2: Recommended Dosage Modifications for Adverse Reactions

Event	Adverse Reaction Occurrence	Dosage 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%) *[see Adverse Reactions (6.1) in the full Prescribing Information]*. 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 jirovecii* 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 *[see Adverse Reactions (6.1) in the full Prescribing Information]*.

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 to 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 *[see Adverse Reactions (6.1) in the full Prescribing Information]*. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dosage and Administration (2.3) 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 *[see Adverse Reactions (6.1) in the full Prescribing Information]*. 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 *[see Adverse Reactions (6.1) in the full Prescribing Information]*. 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 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 present 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§	39	2.8	35	0	17	1.2
Lower respiratory tract infection¶	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[b]						
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

§ Includes upper respiratory tract infection, nasopharyngitis and sinusitis
[a] Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection
[b] Derived from adverse reaction and laboratory data
[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 to 1.5 to 3 times ULN 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 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[§]	29	1.9	26	3.4	17	2.9
Lower respiratory tract infection[a]	23	6	26	15	14	6
Blood and lymphatic system disorders[b]						
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
§ Includes upper respiratory tract infection, rhinitis and nasopharyngitis
[a] Includes pneumonia, lower respiratory tract infection, bronchitis, bronchiolitis, tracheitis, and lung infection
[b] Derived from adverse reaction and laboratory data
[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 to 4% and 15 to 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 breastfeed while taking CALQUENCE and for 2 weeks after the last dose.

Females and Males of Reproductive Potential

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]*.

Pregnancy Testing

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

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for 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 use of CALQUENCE in patients with severe hepatic impairment (Child-Pugh class C). No dosage adjustment of CALQUENCE is recommended in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. The safety of CALQUENCE has not been evaluated in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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DISCOVER THE CURRENT OF CALQUENCE

Follow the current to the latest long-term efficacy and safety data, now with up to ~6 years of median follow-up*[1]

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SEE MORE INFORMATION AT calquencehcp.com OR SCAN QR CODE

CALQUENCE®
acalabrutinib 100 mg tablets

*At median 74.5-month follow-up (range: 0.0-89.0 months).[1]

Reference: 1. Sharman JP, et al. Abstract 636. Presented at: 2023 ASH Annual Meeting. December 9-12.

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