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

January/February 2026 Volume 24, Issue 1, Supplement 1

A SPECIAL MEETING REVIEW EDITION

Highlights in Chronic Lymphocytic Leukemia From the 67th ASH Annual Meeting and Exposition

A Review of Selected Presentations From ASH 2025 • December 6-9, 2025 • Orlando, Florida

Special Reporting on:

- Post Hoc Safety Analysis and Exploratory Analysis of Impact of Prognostic Mutations on Outcomes of Fixed-Duration Acalabrutinib-Venetoclax Combinations vs Chemoimmunotherapy: Results From the Phase 3 AMPLIFY Trial
- Fixed-Duration vs Continuous Targeted Treatment for Previously Untreated CLL: Results From the Randomized CLL17 Trial
- Pirtobrutinib vs Bendamustine + Rituximab in Patients With CLL/SLL: First Results From a Randomized Phase 3 Study Examining a Non-covalent BTK Inhibitor in Untreated Patients
- Pirtobrutinib vs Ibrutinib in Treatment-Naïve and Relapsed/Refractory CLL/SLL: Results From the First Randomized Phase 3 Study Comparing a Non-covalent and Covalent BTK Inhibitor
- Efficacy of Second-Line Treatment in CLL After Venetoclax-Based First-Line Treatment: Results From the GAIA/CLL13 Trial
- Time-Limited Acalabrutinib Monotherapy in Frail Patients With Previously Untreated CLL: Primary Endpoint Analysis of the Randomized STAIR trial
- Long-Term Immune Reconstitution and Final 1-Year Follow-up After Fixed-Duration Venetoclax-Obinutuzumab in First-Line CLL: Results From the Phase 3 CRISTALLO trial
- MRD-Guided Ibrutinib + Venetoclax Improves Outcomes in CLL Patients With *TP53*, *ATM*, or *NOTCH1* Aberrations Compared to Ibrutinib and FCR: Results From the Phase 3 NCRI FLAIR Trial

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Post Hoc Safety Analysis and Exploratory Analysis of Impact of Prognostic Mutations on Outcomes of Fixed-Duration Acalabrutinib-Venetoclax Combinations vs Chemoimmunotherapy: Results From the Phase 3 AMPLIFY Trial

The phase 3 AMPLIFY trial compared fixed-duration acalabrutinib plus venetoclax with or without obinutuzumab against chemoimmunotherapy in fit patients with previously untreated chronic lymphocytic leukemia (CLL) without del(17p) or *TP53* mutations. As previously reported, the acalabrutinib-containing regimens were associated with a significant progression-free survival (PFS) benefit over chemoimmunotherapy; estimated 3-year PFS rates were 76.5% with acalabrutinib-venetoclax (AV), 83.1% with acalabrutinib, venetoclax, and obinutuzumab (AVO), and 66.5% with chemoimmunotherapy.[1]

Post Hoc Safety Analysis

At the 67th American Society of Hematology Annual Meeting and Exposition (henceforth referred to as ASH 2025), Seymour and colleagues presented results of a post hoc safety analysis from AMPLIFY further assessing the safety of AV, AVO, and chemoimmunotherapy.[2] The trial enrolled 834 patients who were randomly assigned and received at least 1 dose of AV (n=291), AVO (n=284), or chemoimmunotherapy (n=259). Patients assigned to AV received acalabrutinib in cycles 1 through 14 and venetoclax in cycles 3 through 14; patients assigned to AVO also received obinutuzumab in cycles 2 through 7. Chemoimmunotherapy consisted of investigator's choice of fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine-rituximab (BR) administered for 6 cycles.

Treatment exposure varied across arms, with a median duration of acalabrutinib exposure of 12.9 months in the AV and AVO arms, compared with a median treatment exposure of 5.6 months in the FCR/BR arm.

Table 1. Exposure-Adjusted Event Rates for Events of Clinical Interest in the AMPLIFY Trial

Events per 100 person-months	AV (n=291)		AVO (n=284)		FCR/BR (n=259)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE of clinical interest	25.275	11.706	36.098	18.895	57.791	38.123
Cardiac events	0.831	0.126	1.110	0.211	0.855	0.285
Anemia	0.680	0.378	0.396	0.159	1.853	1.283
Leukopenia	5.790	4.531	8.826	7.029	19.382	15.392
Thrombocytopenia	0.529	0.151	1.691	1.163	3.563	2.280
Hemorrhage	3.323	0.076	4.704	0.185	0.926	0.071
Hepatotoxicity	0.705	0.302	0.714	0.238	1.354	0.285
Hypertension	0.302	0.201	0.317	0.185	0.570	0.143
Infections	6.470	1.032	8.377	2.193	8.765	2.138
Interstitial lung disease/ pneumonitis	0	0	0.132	0	0.071	0.071
Secondary primary malignancies	0.453	0.126	0.317	0.132	0.143	0
Tumor lysis syndrome	0.025	0.025	0.026	0.026	0.570	0.570

AV, acalabrutinib-venetoclax; AVO, acalabrutinib, venetoclax, and obinutuzumab; BR, bendamustine-rituximab; FCR, fludarabine, cyclophosphamide, and rituximab; TEAE, treatment-emergent adverse event.

Adapted from Seymour J et al. Presented at: 67th American Society of Hematology Annual Meeting and Exposition; December 6-9, 2025; Orlando, Florida, USA. Abstract 2118.[2]

The incidence of any-grade events of clinical interest was 76.3% with AV, 85.2% with AVO, and 71.4% with FCR/BR. Exposure-adjusted event rates (EAERs) were 25.3, 36.1, and 57.8 events per 100 person-months, respectively (Table 1). Rates of any-grade cardiac events were higher with AV (9.3%) or AVO (12.0%) compared with FCR/BR (3.5%), with both comparisons reaching significance (P=.0063 and P=.0003). However, the EAER was similar across arms, at 0.83, 1.11, and 0.86 events per 100 person-months with AV, AVO, and FCR/BR, respectively. Grade 3 or greater cardiac events were infrequent across arms, with EAERs of 0.126, 0.211, and 0.285 events per 100 person-months, respectively.

The incidence of infection was higher with AV (50.9%) and AVO (53.9%) compared with FCR/BR (31.7%; P<.0001 for both comparisons); however, EAERs were similar across arms, at 6.47, 8.38, and 8.77 events per 100 person-months with AV, AVO, and FCR/BR, respectively. EAERs for grade 3 or greater infections were 1.032, 2.193, and 2.138 events per 100 person-months, respectively, indicating a lower adjusted incidence of grade 3 or greater infections in the AV arm. Requirements for granulocyte colony-stimulating factor were lower with AV and AVO (30.9% and 42.6%, respectively) compared with FCR/BR (57.1%).

In subgroup analysis, the rate of grade 3 or greater infection was increased in the AVO arm among patients with a baseline immunoglobulin G (IgG) level of at least 600 mg/dL (above the lower limit of normal) but was similar across arms among patients with a baseline IgG of 400 mg/dL or less. Cumulative rates of second primary malignancies were similar across arms, with basal cell carcinoma being the most frequently reported across arms. The rate of grade 5 treatment-emergent adverse events (TEAEs) was 3.4% with AV, 6.0% with AVO, and 3.5% with FCR/BR; these were primarily attributed to COVID-19.

Overall, 91.6% of patients in the AV arm and 94.9% of patients in the AVO arm completed treatment. The incidence of premature discontinuation of all study drugs or death was lower with AV vs FCR/BR (8.4% vs 18.6%; hazard ratio [HR] for time to an event, 0.07; P<.0001) and with AVO vs FCR/BR (5.1% vs 18.6%; HR for time to an event, 0.16; P<.0001). Adverse events (AEs) were the most common cause of discontinuation of all study drugs, reported in 5.9%, 4.3%, and 10.5% of patients in the AV, AVO, and FCR/BR arms, respectively. The incidence of AEs leading to withholding and reduction of doses was 49.8% and 14.1%, respectively, in the AV arm; 64.8% and 20.8%, respectively, in the AVO arm; compared with 31.3% and 11.2%, respectively, in the FCR/BR arm.

An efficacy analysis including patients who completed treatment and had at least 14 months of follow-up found that dose modifications did not appear to negatively affect efficacy of the acalabrutinib-containing regimens. Among patients receiving AV, the estimated 24-month PFS rate from the end of treatment was 77.0% in patients with dose modifications (n=125) and 80.1% in patients without dose modifications (n=127). Among patients receiving AVO, estimated 24-month PFS rates from the end of treatment were 91.2% in patients with dose modifications (n=124) and 94.4% in patients without dose modifications (n=93). Similar patterns were noted for the time to next treatment (TTNT).

Investigators also reported the incidence of tumor lysis syndrome (TLS) and the effect of the acalabrutinib lead-in period on TLS risk. At baseline, 93 patients in the AV arm (32.0%), 75 patients in the AVO arm (26.4%), and 86 patients in the FCR/BR arm (33.2%) had a high risk of TLS. At cycle 3, most patients with high TLS risk had moved to the medium-risk category (60.2%, 21.3%, and 8.1%, respectively) or to the low-risk category (19.4%, 61.3%, and 77.9%, respectively). TLS occurred in 1 patient receiving AV during the venetoclax ramp-up and in 1 patient receiving AVO during the acalabrutinib lead-in; both were laboratory events with no clinical TLS reported.

Exploratory Analysis of Impact of Prognostic Mutations on Outcomes

In the GAIA/CLL13 trial, established prognostic factors including unmutated IGHV (uIGHV) and the presence of *NOTCH1* mutations were associated with shorter PFS after either chemoimmunotherapy or venetoclax-based targeted therapy.[3] At ASH 2025, Ghia and colleagues presented an exploratory analysis from the AMPLIFY trial evaluating the association between prognostic genetic factors and clinical outcomes with acalabrutinib-containing regimens vs chemoimmunotherapy in patients with treatment-naive CLL.[4] Using next-generation sequencing (NGS), investigators evaluated the prognostic significance of 6 genes with established prognostic value in the context of chemoimmunotherapy: *ATM, SF3B1, NOTCH1, BIRC3, MYD88,* and *CARD11,* and IGHV status.[5,6]

The overall prevalence of uIGHV was 59%. Approximately one-half of patients had at least 1 key mutation, with mutations most commonly occurring in *ATM* (20%-24% across arms), *SF3B1* (15%-16%), and *NOTCH1* (14%-17%). Mutations were more commonly found in patients with uIGHV than in patients with mutated IGHV (mIGHV) except for *MYD88* mutations, which occurred more frequently in patients with mIGHV. Co-mutations included *ATM/SF3B1,* detected in 10% to 12% of patients, *ATM/NOTCH1*, detected in 6% to 10%, and *NOTCH1/SF3B1*, detected in 5% to 9%.

In the intention-to-treat (ITT)

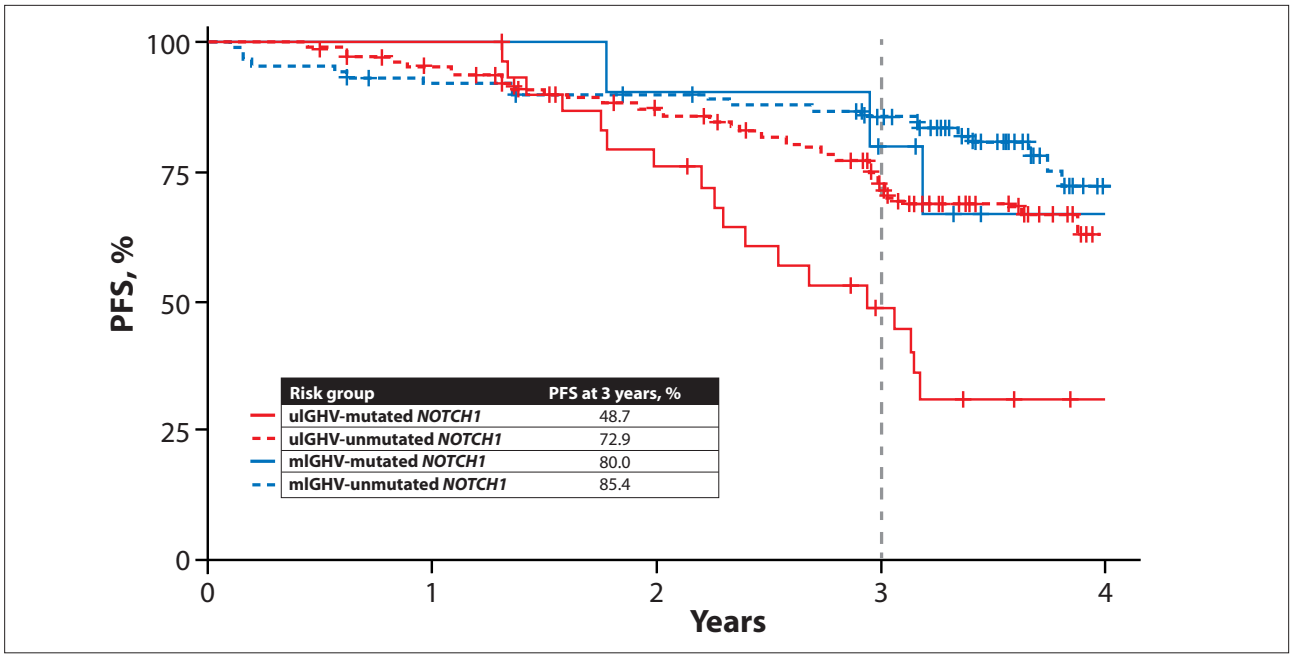

Figure 1. PFS for uIGHV and mIGHV subgroups with and without *NOTCH1* in the AV arm.

AV, acalabrutinib-venetoclax; mIGHV, mutated IGHV; PFS, progression-free survival; uIGHV, unmutated IGHV.

Adapted from Ghia P et al. Presented at: 67th American Society of Hematology Annual Meeting and Exposition; December 6-9, 2025; Orlando, Florida, USA. Abstract 3898.[4]

population, 36-month PFS rates were higher with AV (76.5%) and AVO (83.1%) compared with FCR/BR (66.5%). Among patients with uIGHV, the HR for PFS with AV vs FCR/BR was 0.69 (95% CI, 0.48-0.97) and the HR for PFS with AVO vs FCR/BR was 0.35 (95% CI, 0.23-0.53). The PFS benefit with AV or AVO vs FCR/BR was consistently maintained across prespecified mutation status subgroups.

Among patients receiving AV, *NOTCH1* mutations were associated with a lower 36-month PFS rate (57.1% vs 79.0% in patients without *NOTCH1* mutations). However, *NOTCH1* mutations were not prognostic in the AVO arm. Mutations in *ATM* and *SF3B1* were not prognostic in the AV or AVO arms.

In the AV arm, PFS rates in the uIGHV subgroup were higher among patients without a co-occurring *NOTCH1* mutation than in patients with a co-occurring *NOTCH1* mutation (36-month PFS, 72.9% vs 48.7%); conversely, in the mIGHV subgroup, 36-month PFS rates were 85.4% and 80%, respectively (Figure 1). However, investigators cautioned that the mIGHV, *NOTCH1*-mutated subgroup had a small patient population.

In the AVO arm, the presence of *NOTCH1* mutations did not appear to affect PFS outcomes across IGHV status. In the FCR/BR arm, PFS rates were lower in the *NOTCH1*-mutated uIGHV subgroup vs the *NOTCH1*-mutated mIGHV subgroup, although number of patients in each subgroup was low.

Acalabrutinib-containing regimens were also associated with an improvement in TTNT compared with chemoimmunotherapy, with 36-month TTNT rates of 88.5% with AV, 85.4% with AVO, and 75.2% with FCR/BR, yielding HRs of 0.46 (95% CI, 0.32 to 0.64) with AV or AVO vs FCR/BR. In subgroup analyses, the TTNT benefit with AV or AVO vs BR was consistent regardless of the presence of key mutations and was observed in the uIGHV and mIGHV subgroups. Among patients receiving AV or FCR/BR with uIGHV, there was a trend toward shorter TTNT in patients with a *NOTCH1* mutation. TTNT did not appear to be affected by *NOTCH1* status in the mIGHV subgroup, but those patient populations were small.

In a univariate Cox regression analysis, genetic alterations that were significantly prognostic for PFS varied by arm and included IGHV status in the AV and FCR/BR arms, *BIRC3* and *NOTCH1* in the AV arm, and *SF3B1* in the FCR/BR arm. In a multivariate Cox regression analysis, factors that were significantly prognostic for PFS included *NOTCH1* and the presence of bulky disease in the AV arm, bulky disease and age in the AVO arm, and IGHV status and del(11q) in the FCR/BR arm.

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A key practical safety insight from the AMPLIFY trial is the effect of the acalabrutinib lead in on tumor lysis risk. After 2 cycles, more than 90% of patients shifted from high to low or intermediate TLS risk, making venetoclax initiation substantially safer. This also offers flexibility in routine practice. If lymphocytosis persists after 2 months and TLS risk remains a concern, extending the lead in to a third cycle is reasonable and easily implemented. By that point, most patients will have a sufficiently low TLS risk to proceed safely with venetoclax. The main interpretation of the exploratory analysis from the AMPLIFY trail is that in patients with high-risk mutations, clearly targeted therapy is preferable to chemoimmunotherapy.

—Susan O'Brien, MD

Fixed-Duration vs Continuous Targeted Treatment for Previously Untreated CLL: Results From the Randomized CLL17 Trial

Current options for first-line CLL therapy include a continuous Bruton tyrosine kinase (BTK) inhibitor and a fixed-duration regimen of a BCL2 inhibitor in combination with an anti-CD20 antibody or a BTK inhibitor.[1] These approaches have not been compared in a head-to-head randomized trial. To prospectively evaluate the efficacy and safety of these 2 approaches, the investigator-initiated, randomized, phase 3 CLL17 trial was undertaken to compare indefinite ibrutinib against fixed-duration venetoclax-obinutuzumab or venetoclax-ibrutinib in patients with previously untreated CLL. Results from CLL17 were presented at ASH 2025 and published concurrently in the *New England Journal of Medicine*.[2,3]

Between February 2021 and November 2022, 976 patients were screened across 174 sites in 13 countries. Patients were stratified 1:1:1 according to fitness, del(17p)/*TP53* mutation, and IGHV status, and randomly assigned to ibrutinib 420 mg daily until progression (n=301), venetoclax 400 mg daily (cycle 1 day 22 to cycle 12) plus obinutuzumab 1000 mg intravenous (IV) (cycle 1 day 1/2, 8, and 15, and cycles 2-6 day 1) (n=303), or venetoclax 400 mg daily (cycle 4 day 1 to cycle 15) plus ibrutinib 420 mg daily (cycle 1 day 1 to cycle 15) (n=305).

After a median follow-up of 34.2 months, the trial met its primary objective, demonstrating a noninferior PFS with fixed-duration venetoclax-obinutuzumab vs continuous ibrutinib (HR, 0.87; 98.3% CI, 0.54-1.41), and with fixed-duration venetoclax-ibrutinib vs continuous ibrutinib (HR, 0.84; 98.0% CI, 0.53-1.32) (Table 2). The 3-year PFS rates were 81.1% with venetoclax-obinutuzumab, 79.4% with venetoclax-ibrutinib, and 81.0% with ibrutinib. Investigators noted that additional follow-up is needed to assess differences in PFS between arms across clinical and biologic subgroups.

Rates of undetectable minimal residual disease (MRD) at the end of treatment were 73.3% with venetoclax-obinutuzumab, 47.2% with venetoclax-ibrutinib, and 0% with ibrutinib; 3-year overall survival (OS) rates were 91.5%, 96.0%, and 95.7%, respectively. Frequent AEs included neutropenia (52.5%, 36.3%, and 16.4% of patients receiving venetoclax-obinutuzumab, venetoclax-

ibrutinib, and ibrutinib, respectively), infections (76.3%, 80.2%, and 79.9%, respectively), and diarrhea (27.1%, 47.2%, and 34.9%, respectively). Rates of atrial fibrillation were 3.7%, 12.5%, and 16.8%, respectively. Grade 3 or greater infections were reported in 34.9% of patients receiving venetoclax-obinutuzumab (15.9% with COVID-19), 25.1% of patients receiving venetoclax-ibrutinib (8.6% with COVID-19), and 24.8% of patients receiving ibrutinib (6.7% with COVID-19).

Investigators noted that all CLL therapies, and particularly anti-CD20 antibodies, are associated with a risk of infection, and that safety outcomes were consistent with the established safety profiles of these regimens. They concluded that fixed-duration treatment is a primary option for most patients with previously untreated CLL.

Table 2. PFS With Fixed-Duration Venetoclax-Obinutuzumab and Venetoclax-Ibrutinib vs Continuous Ibrutinib in Patients With Previously Untreated CLL

Group	**PFS at 3 years, %**
Continuous ibrutinib	81.0%
Venetoclax-ibrutinib	79.4%
Venetoclax-obinutuzumab	81.1%
Comparison	**HR**
Venetoclax-ibrutinib vs continuous ibrutinib	0.84
Venetoclax-obinutuzumab vs continuous ibrutinib	0.87

CLL, chronic lymphocytic leukemia; HR, hazard ratio; PFS, progression-free survival.

Adapted from Al-Sawaf O et al. Presented at: 67th American Society of Hematology Annual Meeting and Exposition; December 6-9, 2025; Orlando, Florida, USA. Abstract 1.[2]

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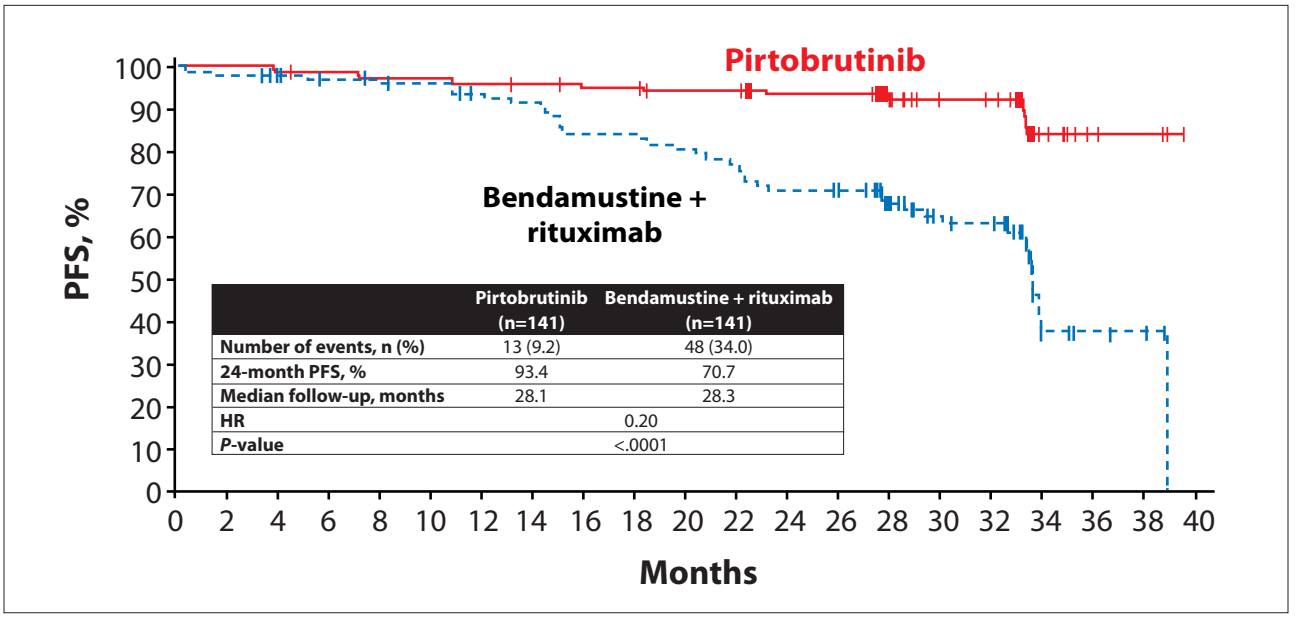
The main limitation of the CLL17 trial is the short follow-up. Frontline CLL therapies are associated with long remissions, so at 3 years it is expected that outcomes appear similar across treatment arms. With extended follow-up, differences will likely emerge, potentially by biologic subgroup. For now, choosing fixed-duration therapy is reasonable, given its reduced drug exposure, lower toxicity risk, and financial advantages. The higher rate of cardiac events with continuous ibrutinib further highlights the toxicity of continuous therapy.

—Susan O'Brien, MD

Pirtobrutinib vs Bendamustine + Rituximab in Patients With CLL/SLL: First Results From a Randomized Phase 3 Study Examining a Noncovalent BTK Inhibitor in Untreated Patients

Pirtobrutinib is a noncovalent BTK inhibitor that is approved by the US Food and Drug Administration for use in adults with CLL or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a covalent BTK inhibitor and a BCL2 inhibitor.[1] Previously, the efficacy and safety of noncovalent BTK inhibitors including pirtobrutinib had not been directly compared against current standard therapies for the initial treatment of CLL. Two recent prospective trials directly compared pirtobrutinib against current therapies in patients with treatment-naive CLL. BRUIN CLL-314 compared pirtobrutinib with ibrutinib in previously untreated and relapsed/refractory (R/R) CLL. In the subset of patients with previously



	Pirtobrutinib (n=141)	Bendamustine + rituximab (n=141)
Number of events, n (%)	13 (9.2)	48 (34.0)
24-month PFS, %	93.4	70.7
Median follow-up, months	28.1	28.3
HR	0.20	
P-value	<.0001	

Figure 2. PFS in the BRUIN CLL-313 trial of pirtobrutinib vs bendamustine + rituximab in patients with previously untreated CLL/SLL.

CLL, chronic lymphocytic leukemia; HR, hazard ratio; PFS, progression-free survival; SLL, small lymphocytic lymphoma.

Adapted from Jurczak W et al. Presented at: 67th American Society of Hematology Annual Meeting and Exposition; December 6-9, 2025; Orlando, Florida, USA. Abstract LBA-3.[3]

untreated CLL (n=225), the overall response rate (ORR) as assessed by independent review committee (IRC) was 92.9% with pirtobrutinib and 85.9% with ibrutinib; investigator-assessed PFS favored pirtobrutinib over ibrutinib (HR, 0.24; 95% CI, 0.10-0.59).[2]

At ASH 2025, Jurczak and colleagues presented results from the randomized, open-label, global, phase 3 BRUIN CLL-313 trial comparing pirtobrutinib with BR in patients with previously untreated CLL/SLL.[3] The trial enrolled 282 patients with treatment-naive CLL/SLL without del(17p) who were stratified by IGHV mutation status and Rai stage (0-II vs III-IV) and randomly assigned them to pirtobrutinib (200 mg once daily) (n=141) or BR (bendamustine 90 mg/m^2 IV plus rituximab 375-400 mg/m^2 IV) for 6 cycles (n=141). Crossover from BR to pirtobrutinib was allowed upon disease progression confirmed by IRC.

In the pirtobrutinib arm, 140 patients (99.3%) started treatment and 11.3% discontinued treatment, primarily owing to AEs (4.3%), with the remaining 87.9% continuing treatment. In the BR arm, 132 patients (93.6%) started treatment, 102 patients (72.3%) completed treatment, and 30 patients (21.3%) discontinued early, primarily owing to AEs (12.7%). The median time on treatment was 32.3 months for pirtobrutinib and 5.6 months for BR. Of the 34 patients with disease progression on the BR arm, 18 patients (52.9%) crossed over to pirtobrutinib.

After a median follow-up of 28 months, pirtobrutinib was associated with a significant reduction in risk of progression or death compared with BR; the 24-month PFS rate was 93.4% with pirtobrutinib vs 70.7% with BR (HR, 0.20; 95% CI, 0.11-0.37; *P*<.0001) (Figure 2). Subgroup analyses favored pirtobrutinib in all prespecified groups, including in patients with mIGHV and uIGHV, in patients with complex karyotype, and in patients with *TP53* mutations. The IRC-assessed ORR was 94.3% with pirtobrutinib (13.5% complete response [CR] or incomplete CR [CRi]) and 80.9% with BR (20.6% CR/CRi).

OS outcomes were immature, but investigators noted a nonsignificant trend toward improved OS with pirtobrutinib vs BR (24-month OS rate, 97.8% vs 93.0%; HR, 0.26; 95% CI, 0.07-0.93; stratified log-rank 2-sided *P*=.0261), despite the 52.9% crossover rate.

The most frequent TEAEs reported with pirtobrutinib were COVID-19 (21.4%; 0.7% grade ≥3), upper respiratory tract infection (17.9%; 0.7% grade ≥3), and neutropenia (12.1%; 7.1% grade ≥3). The most frequent TEAEs reported with BR were neutropenia (38.6%; 34.8% grade ≥3), nausea (23.5%; 0.8% grade ≥3), pyrexia (18.9%; 0% grade ≥3), anemia (15.9%; 7.6% grade ≥3), and infusion-related reaction (15.2%; 3.0% grade ≥3).

Exposure-adjusted incidence rates

were lower with pirtobrutinib compared with BR across AEs, including for neutropenia (5.2 vs 110.0 per 100 person-years), upper respiratory tract infection (7.7 vs 15.7 per 100 person-years), and COVID-19 (9.9 vs 20.9 per 100 person-years). Pirtobrutinib was also associated with reductions over BR in rates of discontinuation owing to TEAEs (4.3% vs 15.4%) and dose reduction owing to TEAEs (3.6% vs 31.1%).

Atrial fibrillation and flutter occurred in 1.4% of patients on the pirtobrutinib arm (0.7% grade ≥3) and 1.5% of patients on the BR arm (0.8% grade ≥3) and remained low in the subset of patients aged 75 years or older, with an overall incidence of 5.0% with pirtobrutinib and 4.3% with BR, and no grade 3 or greater events reported.

Investigators concluded that in patients with treatment-naive CLL/SLL, pirtobrutinib was associated with superior PFS vs BR, a trend toward longer OS, and a good tolerability profile, suggesting that pirtobrutinib may be considered a new standard of care for the initial treatment of CLL, particularly for older patients who may receive only a single line of therapy.

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This trial is important because it will likely support frontline approval of pirtobrutinib in the United States. The central question, however, is whether it should be used first line. Covalent BTK inhibitors provide long remissions, and pirtobrutinib remains effective after covalent inhibitor exposure. What is still unknown given the short follow-up is the durability of frontline pirtobrutinib and whether covalent inhibitors would retain efficacy afterward. As the authors note, pirtobrutinib may be a reasonable frontline option for older patients expected to receive only 1 line of therapy, where its more favorable safety profile is a clear advantage.

—Susan O'Brien, MD

Pirtobrutinib vs Ibrutinib in Treatment-Naïve and Relapsed/Refractory CLL/SLL: Results From the First Randomized Phase 3 Study Comparing a Non-covalent and Covalent BTK Inhibitor

The first-generation BTK inhibitor ibrutinib and the second-generation BTK inhibitors acalabrutinib and zanubrutinib have improved outcomes and transformed the care of patients with CLL. However, these agents are associated with limitations including toxicities, short half-lives, and the development of resistance mutations, in particular *C481S*.[1]

Pirtobrutinib is a noncovalent BTK inhibitor that binds reversibly but with a long half-life, allowing for sustained BTK inhibition.[2] In the BRUIN CLL-321 trial, pirtobrutinib demonstrated improved PFS and a favorable safety profile compared with chemoimmunotherapy in patients with CLL/SLL previously treated with a covalent BTK inhibitor.[3] The efficacy and safety of pirtobrutinib in treatment-naive patients has not been established.

The randomized, phase 3 BRUIN CLL-314 trial was undertaken to compare pirtobrutinib with ibrutinib in 2 population of patients with CLL: treatment-naive patients and patients with R/R CLL not previously treated with a BTK inhibitor. Results were presented at ASH 2025 and concurrently published in the *Journal of Clinical Oncology* (Table 3).[4,5] The trial enrolled 662 patients who were stratified by the presence of del(17p) and the number of prior lines of therapy (0 vs 1 vs ≥2) and randomly assigned to pirtobrutinib 200 mg once daily (n=331) or ibrutinib 420 mg once daily (n=331). Overall, 34% of patients were treatment naive.

In a blinded IRC analysis, pirtobrutinib demonstrated a numerically higher and statistically noninferior

Table 3. IRC-Assessed ORR With Pirtobrutinib and Ibrutinib in the BRUIN CLL-314 Trial

	ITT population		TN population		R/R population	
	Pirtobrutinib (n=331)	Ibrutinib (n=331)	Pirtobrutinib (n=112)	Ibrutinib (n=113)	Pirtobrutinib (n=219)	Ibrutinib (n=218)
ORR (PR or better), %	87.0	78.5	92.9	85.8	84.0	74.8
Best overall response, %						
CR or CRi	4.8	2.4	7.1	3.5	3.7	1.8
PR or nPR	82.2	76.1	85.7	82.3	80.4	72.9
PR-L	2.4	3.9	0.9	2.7	3.2	4.6
SD	5.4	10.9	2.7	4.4	6.8	14.2
PD	1.5	1.2	0	0	2.3	1.8

CR, complete remission, CRi, incomplete CR; IRC, independent review committee; ITT, intention-to-treat; nPR, nodular partial remission; ORR, overall response rate; PD, progressive disease; PR, partial remission; PR-L, partial remission with lymphocytosis; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive.

Adapted from Woyach J et al. Presented at: 67th American Society of Hematology Annual Meeting and Exposition; December 6-9, 2025; Orlando, Florida, USA. Abstract 683.[4]

ORR compared with ibrutinib in the ITT population (87.0% vs 78.5%; nominal *P*=.0035) and the R/R population (84.0% vs 74.8%; nominal *P*=.0175). In the treatment-naive subgroup, the ORR with pirtobrutinib and ibrutinib was 92.9% and 85.8%, respectively (nominal *P*=.0886). ORRs were generally higher with pirtobrutinib over ibrutinib across key clinical and demographic subgroups and in high-risk subsets, including patients with del(17p), uIGHV, and complex karyotype.

PFS outcomes favored pirtobrutinib over ibrutinib in the treatment-naive subgroup (18-month PFS, 95.3% vs 87.6%; HR, 0.239; 95% CI, 0.098-0.586; nominal *P*=.0007) and in the R/R subgroup (18-month PFS, 81.7% vs 79.2%; HR, 0.729; 95% CI, 0.471-1.128; nominal *P*=.1563).

In the safety analysis, the most common grade 3 or greater AEs with pirtobrutinib and ibrutinib were neutropenia (17.3% and 13.2%, respectively), pneumonia (6.4% and 8.6%, respectively), and anemia (5.8% and 3.7%, respectively). Atrial fibrillation occurred in 2.4% of patients receiving pirtobrutinib (0.9% grade ≥3) compared with 13.5% of patients receiving ibrutinib (4.0% grade ≥3). In patients aged 75 years or older, rates of atrial fibrillation/flutter were 4.5% with pirtobrutinib (1.5% grade ≥3) and 21.4% with ibrutinib (7.1% grade ≥3). Pirtobrutinib was also associated with a lower rate of dose reductions than ibrutinib (7.9% vs 18.2%) and a lower rate of discontinuation (9.4% vs 10.8%).

Investigators noted that this trial was the first to compare a noncovalent BTK inhibitor with a covalent BTK inhibitor in CLL and the first to compare 2 BTK inhibitors head-to-head in treatment-naive patients with CLL. Pirtobrutinib demonstrated noninferior ORR to ibrutinib in the ITT and R/R populations, a trend toward a PFS benefit in the R/R and treatment-naive populations, and a favorable tolerability profile.

These results are notable, as pirtobrutinib appears to perform at least as well as covalent BTK inhibitors in both relapsed and frontline settings. They also highlight the unresolved question of sequencing. Pirtobrutinib is active after covalent BTK inhibitor failure, but if frontline use yields very long remissions, the role of covalent inhibitors afterward may diminish. For now, the follow-up is too short to assess the durability of frontline pirtobrutinib.

—Susan O'Brien, MD

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Efficacy of Second-Line Treatment in CLL After Venetoclax-Based First-Line Treatment: Results From the GAIA/CLL13 Trial

Outcomes with second-line therapy after first-line venetoclax-based therapy have not been well characterized, as most clinical trial data in R/R CLL have been derived from patients who have received chemoimmunotherapy in prior lines of therapy. In a substudy of the MURANO trial, retreatment with fixed-duration venetoclax-rituximab in 25 patients with relapsed CLL was associated with a median PFS of 23 months and an ORR of 72%.[1] Retrospective data from 23 patients with R/R CLL who received a BTK inhibitor after developing disease progression on venetoclax-based therapy reported a median PFS of 34 months after starting a BTK inhibitor.[2]

The randomized, open-label, phase 3 GAIA/CLL13 trial compared 3 first-line venetoclax-containing combinations in 926 fit patients with CLL without *TP53* mutations: rituximab-venetoclax (RV), venetoclax-obinutuzumab (VO), and venetoclax, obinutuzumab, and ibrutinib (VOI), and compared these against chemoimmunotherapy (CIT). As previously reported, venetoclax-obinutuzumab with or without ibrutinib was associated with superior PFS and higher rates of MRD compared with chemoimmunotherapy.[3]

At ASH 2025, Niemann and colleagues reported efficacy outcomes for 177 patients from the GAIA/CLL13 trial who received second-line treatment after developing progressive disease on their assigned first-line regimens (Table 4).[4] The median time from disease progression to the start of second-line therapy or death ranged from 10.1 months after first-line CIT to 14.5 months after first-line VOI.

Table 4. TFS Rates From Second-Line Treatment in Fit Patients With *TP53*-Wild Type CLL Receiving First-Line Venetoclax-Based Therapy

Second-line treatment	n	1-year rate	2-year rate
Venetoclax + BTK inhibitor	26	100.0	100.0
Venetoclax based	23	95.0	81.4
BTK inhibitor based	57	80.7	77.9
Chemoimmunotherapy	6	27.8	27.8

CLL, chronic lymphocytic leukemia; HR, hazard ratio; TFS, treatment-free survival.

Adapted from Niemann C et al. Presented at: 67th American Society of Hematology Annual Meeting and Exposition; December 6-9, 2025; Orlando, Florida, USA. Abstract 795.[4]

Among 65 patients who had received first-line CIT, the most common second-line regimens included BTK inhibitor-based therapy (52%) and venetoclax-based therapy (34%), followed by venetoclax plus a BTK inhibitor (8%) and CIT (2%). Among 63 patients who had received first-line RV, second-line regimens included BTK inhibitor–based therapy (56%), venetoclax-based therapy (22%), venetoclax plus a BTK inhibitor (17%), and CIT. Among 32 patients who had received first-line VO, second-line therapy included venetoclax plus a BTK inhibitor (47%), BTK inhibitor–based therapy (34%), venetoclax-based therapy (13%), and CIT (6%). Among 17 patients who had received first-line VOI, second-line therapy included BTK inhibitor–based therapy (65%), venetoclax-based therapy (29%), and CIT (6%).

The proportion of patients alive and not requiring third-line treatment, reported as treatment-free survival 2 (TFS2), across second-line treatments was numerically higher in patients who had received first-line venetoclax-based therapy vs those who had received first-line CIT, with 2-year TFS2 rates of 81.5% and 77.6%, respectively.

Evaluating second-line treatments independent of first-line therapy, TFS2 rates at 2 years were 88.5% with second-line venetoclax plus a BTK inhibitor, 90.5% with second-line venetoclax-based therapy, 76.6% with second-line BTK inhibitor–based therapy, and 21.4% with second-line CIT.

In the subset of patients who had received venetoclax-based first-line therapy, 2-year TFS2 rates were 100% with second-line venetoclax plus a BTK inhibitor, 81.4% with second-line venetoclax-based therapy, 77.9% with second-line BTK inhibitor–based therapy, and 27.8% with CIT (Table 4).

OS from second-line treatment (OS2) rates at 2 years were 92.4% with second-line venetoclax plus a BTK inhibitor, 100% with second-line venetoclax-based therapy, 91.3% with second-line BTK inhibitor–based therapy, and 60% with second-line

CIT.

The investigators concluded that venetoclax-based retreatment is feasible following progression after first-line venetoclax-based first-line treatment in patients with *TP53*-wild type CLL, with 2-year TFS2 rates exceeding 80%. They added that venetoclax plus a BTK inhibitor should be an option for second-line therapy after venetoclax plus an anti-CD20 antibody, and noted that there is no role for CIT in the second-line treatment of CLL.

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The GAIA/CLL13 trial reinforces that chemoimmunotherapy produces poor outcomes when used as second-line treatment. Its role in the frontline setting remains debatable, and in some regions it continues to be used primarily because of lower cost relative to targeted therapy. However, once patients require second-line therapy, the results with chemoimmunotherapy are consistently dismal, supporting the broad conclusion that it should not be used in that setting.

—Susan O'Brien, MD

Time-Limited Acalabrutinib Monotherapy in Frail Patients With Previously Untreated CLL: Primary Endpoint Analysis of the Randomized STAIR trial

Continuous treatment with a covalent BTK inhibitor is a guideline-recommended initial treatment option for patient with CLL.[1] However, indefinite use of BTK inhibitors is associated with a risk of resistance and cumulative toxicity that can be particularly challenging in older or frail adults.[2,3]

Fixed-duration combination therapies have emerged as an alternative to indefinite BTK inhibitor therapy; guideline-recommended combination options include a BTK inhibitor plus a BCL2 inhibitor (eg, venetoclax).[1] However, toxicity is a consideration with this approach; in the GLOW trial, 75.5% of older patients receiving ibrutinib and venetoclax developed grade 3 or greater AEs.[4] The combination of acalabrutinib and venetoclax was evaluated in the AMPLIFY trial, which enrolled patients with a median age of 61 years, thus the tolerability of this approach in older patients is not well established.[5]

At ASH 2025, Guièze and colleagues presented results of the investigator-sponsored, randomized, phase 2 STAIR trial comparing indefinite vs fixed-duration acalabrutinib in older patients with previously untreated CLL/SLL.[6] The trial enrolled patients aged over 70 years requiring treatment per the iwCLL2 018 criteria, who all received acalabrutinib 100 mg twice daily for 18 months; patients were randomly assigned to stop acalabrutinib after the 18-month treatment period, with the options to restart acalabrutinib for an unlimited period upon progression or to continue acalabrutinib indefinitely. The trial was conducted at 32 French centers and enrolled 159 evaluable patients between October 2021 and June 2023.

Patients were required to have a Cumulative Illness Rating Scale (CIRS) score greater than 6 and/or impaired creatinine clearance (31-69 mL/min) and were stratified by the presence of complex karyotype and *TP53* disruption. The primary endpoint was PFS; secondary endpoints included TTNT, OS, ORR at retreatment, quality of life, safety, and tolerability.

The median age of enrolled patients was 77.0 years (range, 70-96 years); 33% of patients were older than 80 years. Most patients had an Eastern Cooperative Oncology Group performance status of 0 (35.8%) or 1 (57.2%). Comorbidities included a history of cancer in 23.9%, a CIRS score greater than 6 in 58.5%, and a creatinine clearance less than 70 mL/min in 78%. Key genetic features include uIGHV in 59.1% of patients, complex karyotype in 28.7%, del(17p) in 11.9%, and *TP53* mutations in 11.9%.

Of the 159 patients who started acalabrutinib, 38 discontinued, primarily owing to AEs (n=13) or progressive disease (n=10). The remaining

121 patients were randomly assigned to continue acalabrutinib (indefinite treatment; n=41) or discontinue acalabrutinib (fixed duration; n=80).

After a median follow-up of 14.2 months from randomization (at the end of the 18-month treatment period), the 1-year PFS rate was 53.1% with fixed-duration acalabrutinib vs 96.3% with continuous treatment. The 1-year TTNT in the fixed-duration arm was 74.0%. Of the 25 patients who restarted treatment, 24 received acalabrutinib per protocol and 1 received venetoclax. The ORR for retreatment with acalabrutinib was 87.5% (79% partial response).

IGHV mutational status was significantly associated with outcomes, with mIGHV associated with superior outcomes vs uIGHV as assessed by 1-year PFS rate (90.4% vs 34.0%; $P<.001$) and 1-year TTNT (100% vs 62.4%; $P<.001$). At 1 year, OS rates were similar with indefinite vs fixed-duration acalabrutinib, at 100% and 96.8%, respectively.

During the overall treatment period, serious AEs occurred in 30.8% of patients. The most frequent grade 3/4 AEs were neutropenia (12%), thrombocytopenia (3%), anemia (2.5%), increased alanine aminotransferase (2.5%), and fracture (2.5%). Any-grade atrial fibrillation developed in 6.9% of patients. Rates of grade 3/4 hypertension and bleeding were 2.5% and 1.9%, respectively. Infections of any grade developed in 40.9% of patients, with 8.2% grade 3/4. Second primary malignancies were reported in 35 patients (22%), including 23 nonmelanoma skin cancers. During the post-randomization treatment period, AEs of any severity occurred in 68.3% of patients continuing acalabrutinib and in 43.8% of those discontinuing acalabrutinib.

Investigators concluded that administering acalabrutinib for a fixed duration of 18 months was associated with a significant reduction in PFS, and that the effect of acalabrutinib discontinuation was strongly dependent on IGHV mutational status. They added that additional follow-up is needed to confirm the durability of responses after stopping acalabrutinib in patients with mIGHV, observed reductions in AEs over time, observed lack of effect on OS, and the efficacy of acalabrutinib retreatment.

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The STAIR trial's rationale is reasonable. Longer exposure to BTK inhibitors in older adults increases the likelihood of treatment-related toxicity, and prior studies suggest that some patients who discontinue therapy can experience durable remissions. However, the major limitation of this trial is the very early discontinuation at 18 months. For context, in RESONATE 2 the median time to progression with ibrutinib was roughly 9 years, suggesting that a longer fixed-duration strategy, perhaps 3 years, would have been better to balance exposure, toxicity risk, and the potential for sustained disease control.
—Susan O'Brien, MD

Long-Term Immune Reconstitution and Final 1-Year Follow-up After Fixed-Duration Venetoclax-Obinutuzumab in First-Line CLL: Results From the Phase 3 CRISTALLO trial

The combination of venetoclax and obinutuzumab (VO) as first-line therapy for CLL was evaluated in the CLL14 trial, which demonstrated superior PFS with VO compared with CIT in unfit patients with previously untreated CLL, and the phase 3 CRISTALLO trial, which demonstrated higher rates of MRD

negativity with VO compared with CIT in fit patients with previously untreated CLL.[1,2]

At ASH 2025, Jin and colleagues reviewed updated findings from the CRISTALLO trial and presented results of an analysis evaluating immune dynamics during and after VO and their associations with treatment efficacy.[3] Investigators also evaluated correlations between immune recovery and infection outcomes, given that infections are a primary contributor to morbidity and mortality in patients with CLL.[4]

In the CRISTALLO trial, 166 patients with previously untreated CLL, a CIRS score of 6 or less, and a creatinine clearance of at least 70 mL/min without del(17p) or *TP53* mutations were stratified by Binet stage, IGHV mutation status, and age, and randomly assigned to 6 cycles of VO followed by 6 cycles of venetoclax (n=80) or 6 cycles of FCR/BR (n=86). Venetoclax was administered using a 5-week ramp-up period, reaching 400 mg starting at cycle 3 day 1. Obinutuzumab was administered IV for 6 cycles on cycle 1 day 1/2, 8, and 15, and on day 1 of subsequent cycles.

In the primary efficacy analysis, VO was associated with a significant improvement in the rate of undetectable MRD (uMRD) (10^{-4}) over FCR/BR at 15 months (81.3% vs 54.7%; *P*=.0004). The trial was not powered to detect significant differences in PFS, but after a median follow-up of 41 months, there were fewer instances of progression or death with VO vs FCR/BR (14 vs 18; *P*=.3999), and fewer patients had started a new CLL treatment (3 vs 13).

No new safety findings were noted with this additional follow-up. Rates of grade 3 or greater neutropenia were 48.1% with VO and 38.8% with FCR/BR, and rates of grade 3 or greater febrile neutropenia were 6.5% and 8.2%, respectively. The most frequent grade 3 or greater infections were COVID-19, reported in 7.8% of patients receiving VO and 7.1% receiving FCR/BR, and COVID-19 pneumonia, reported in 9.1% and 5.9%, respectively.

The biomarker analysis found that median CD4+ and CD8+ T-cell counts decreased during VO treatment but remained within the normal range. These trends were observed regardless of MRD status. Transient depletion of natural killer cells was observed at 12 months, with subsequent gradual reconstitution. Absolute numbers of CD19+ CLL cells declined during VO treatment, depleting substantially by the 12-month follow-up. In the uMRD group, CD19+ CLL cells remained suppressed out to 36 months, whereas in the detectable MRD group, CD19+ CLL cells were not fully depleted at 12 months and increased by 10-fold by 18 months.

Nonmalignant B cells were not depleted to the same extent as CLL cells and their counts returned to a normal range by 24 months of follow-up. Serum Ig levels recovered in a similar pattern, particularly IgA and IgM levels. In contrast, Ig recovery was slower and less complete in the MRD-positive group.

Light chain restriction was detected at baseline and resolved over time in the uMRD group, reaching and remaining within normal levels through 42 months of follow-up. In contrast, light chains did not normalize in the MRD-detectable group.

Based on their findings, investigators concluded that immune reconstitution can occur with deep remissions in the context of a fixed-duration VO regimen.

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Regarding immune reconstitution, the investigators were appropriately optimistic about recovery after venetoclax; however, a 24-month interval for normalization of nonmalignant B cells is relatively long. This prolonged period of B-cell depletion has important implications, including an increased risk of infection and potentially reduced vaccine responsiveness during recovery.

—Susan O'Brien, MD

MRD-Guided Ibrutinib + Venetoclax Improves Outcomes in CLL Patients With *TP53*, *ATM*, or *NOTCH1* Aberrations Compared to Ibrutinib and FCR: Results From the Phase 3 NCRI FLAIR Trial

The UK National Cancer Research Institute (NCRI) FLAIR trial is a randomized, open-label, adaptive, phase 3 platform trial with a design that has evolved based on emerging evidence on first-line approaches for the treatment of CLL.

The FLAIR trial initially compared ibrutinib plus rituximab (IR) against FCR as first-line therapy in 771 patients 18 to 75 years of age with previously untreated CLL. In this comparison, IR was associated with significant improvements in PFS over FCR (HR, 0.44; 95% CI, 0.23-0.60; *P*<.0001) but no improvements in OS, and there were 8 sudden unexplained or cardiac deaths in the IR arm vs 2 in the FCR arm.[1]

Subsequently the trial was adapted to include single-agent ibrutinib and ibrutinib-venetoclax, with therapy duration guided by MRD. In the ibrutinib-venetoclax arm, patients received 2 months of ibrutinib with venetoclax added for up to 6 years. Therapy duration was defined as the time to achieve uMRD in peripheral blood and bone marrow multiplied by 2. After a median of 43.7 months, MRD-guided ibrutinib-venetoclax was associated with a significant improvement over FCR in PFS (HR, 0.13; 95% CI, 0.07-0.24; *P*<.001) and longer OS (HR, 0.31; 95% CI, 0.15-0.67).[2] After a median follow-up of 62.2 months, 5-year PFS rates were 93.9% with ibrutinib-venetoclax, 79.0% with ibrutinib alone, and 58.1% with FCR. The proportion of patients attaining uMRD in the bone marrow within 2 years was higher with ibrutinib-venetoclax vs ibrutinib (66.2% vs 0%; *P*<.001) and vs FCR (48.3%).

At ASH 2025, Dalal and colleagues presented additional results from the FLAIR trial, focusing on the effect of baseline gene alterations on clinical outcomes across the 4 treatment arms (ibrutinib, IR, ibrutinib-venetoclax, and FCR).[3] Molecular analyses included NGS (n=1474) to identify 33 recurrently mutated genes, fluorescence in situ hybridization (n=1479) using targeted probes for 11q, 17p, 13p, and 12, and analysis of IGHV somatic hypermutation status for 1373 patients.

At baseline, 36% of patients had mIGHV, 36.8% had del(13q), 26.1% had a normal karyotype, 16.1% had del(11q), 14.4% had trisomy 12, and 0.3% of patients had del(17p); the trial excluded patients with more than 20% cells testing del(17p)-positive. Other mutations present at baseline in at least 10% of patients included *SF3B1* in 17.0%, *ATM* in 14.4%, *NOTCH1* in 11.7%.

MRD-guided treatment with ibrutinib-venetoclax was associated with improvements over the other 3 regimens (ibrutinib, IR, and FCR) as assessed by PFS and OS in most genetic subgroups, including patients with uIGHV, *ATM* aberrations, stereotyped subset #2, *SF3B1, NOTCH1,* and *TP53* mutations. Across subgroups, 5-year PFS rates with ibrutinib/venetoclax ranged from 90% to 100%, and 5-year OS rates ranged from 92% to 100%.

Approximately two-thirds of patients in these groups—including 66% of patients with uIGHV, 60% of patients with stereotyped subset #2, 65% of patients with *ATM* aberrations, and 66% of patients with *NOTCH1* mutations—and 50% of patients with *TP53* mutations, attained MRD negativity and stopped treatment within 3 years of starting ibrutinib-venetoclax.

Investigators concluded that MRD-guided ibrutinib plus venetoclax is highly effective in overcoming adverse prognostic factors including uIGHV, stereotyped set #2, and recurrent genetic alterations.

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The NCRI FLAIR trial analysis contains an impressive amount of data, but the key message is straightforward. In patients with high-risk mutations, targeted therapies consistently outperform chemoimmunotherapy, even when compared with the most effective chemoimmunotherapy regimen available (FCR).
—Susan O'Brien, MD

NOTES

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INDICATIONS AND USAGE

Previously Untreated Mantle Cell Lymphoma

CALQUENCE in combination with bendamustine and rituximab is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are ineligible for autologous hematopoietic stem cell transplantation (HSCT).

Previously Treated Mantle Cell Lymphoma

CALQUENCE is indicated for the treatment of adult patients with MCL who have received at least one prior therapy.

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 Administration Instructions

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.

CALQUENCE as Monotherapy

For patients with MCL, 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 Bendamustine and Rituximab

For patients with previously untreated MCL, the recommended dosage of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.

Start CALQUENCE on Day 1 of Cycle 1 (each cycle is 28 days) and administer until disease progression or unacceptable toxicity. Administer bendamustine 90 mg/m^2 on Days 1 and 2 and rituximab 375 mg/m^2 on Day 1 of Cycle 1 and continue for a total of 6 cycles. Patients achieving a response (PR or CR) after the first 6 cycles may receive maintenance rituximab on Day 1 of every other cycle for a maximum of 12 additional doses, starting on Cycle 8 up to Cycle 30 *[see Clinical Studies (14.1) in the full Prescribing Information]*.

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.

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 are provided in Table 2 and 3.

Table 2: Recommended Dosage Modifications for Adverse Reactions in Patients Receiving CALQUENCE Monotherapy and CALQUENCE in Combination with Obinutuzumab

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).

Table 3: Recommended Dosage Modifications for Adverse Reactions in Patients Receiving CALQUENCE in Combination with BR

Adverse Reaction	Severity[a]	Dosage Modification (Starting dosage of CALQUENCE = 100 mg approximately every 12 hours)
Neutropenia[b] *[see Warnings and Precautions (5.4) in the full Prescribing Information]*	Absolute neutrophil count less than 0.5 x 10^9/L for greater than 7 days	Interrupt CALQUENCE. Once toxicity has resolved to Grade ≤ 2, resume CALQUENCE at starting dosage. Upon 2nd or 3rd occurrence, reduce dosage of CALQUENCE to 100 mg once daily.[c] Discontinue CALQUENCE at 4th occurrence. For bendamustine[b]: Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2, resume bendamustine and consider dosage reduction to 70 mg/m^2.[d,e]
Thrombocytopenia[f] *[see Warnings and Precautions (5.4) in the full Prescribing Information]*	Platelet count 25 to 50 x 10^9/L with clinically significant bleeding or platelet count less than 25 x 10^9/L	Interrupt CALQUENCE. Once toxicity has resolved to Grade ≤ 2 or baseline, resume CALQUENCE at starting dosage. If recurrence, reduce dosage of CALQUENCE to 100 mg once daily.[c] Consider discontinuing CALQUENCE at 3rd occurrence. For bendamustine[f]: Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2 or baseline, resume bendamustine and consider dose reduction to 70 mg/m^2.[e]
Non-hematologic adverse reactions *[see Warnings and Precautions (5) in the full Prescribing Information]*	Grade 3 or higher	Interrupt CALQUENCE. Once toxicity has resolved to Grade ≤ 2 or baseline, resume CALQUENCE at starting dosage. If recurrence, reduce dosage of CALQUENCE to 100 mg once daily.[c] Discontinue CALQUENCE at 3rd occurrence of Grade 4 toxicity. For Grade 3 toxicity, consider the risks and benefits of continuing CALQUENCE.

Table 3: Recommended Dosage Modifications for Adverse Reactions in Patients Receiving CALQUENCE in Combination with BR (cont'd)

Adverse Reaction	Severity[a]	Dosage Modification (Starting dosage of CALQUENCE = 100 mg approximately every 12 hours)
Non-hematologic adverse reactions *[see Warnings and Precautions (5) in the full Prescribing Information]* (cont'd)	Grade 3 or higher	For bendamustine: Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2 or baseline, resume bendamustine and consider dose reduction to 70 mg/m^2.[e]

[a] Graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
[b] For neutropenia with ANC less than 1 x 10^9/L, consideration for bendamustine dose interruption and dosage reduction to 70 mg/m^2 may be appropriate in certain circumstances.
[c] Dose may be re-escalated at the discretion of the physician if patient tolerates a reduced dose for ≥4 weeks.
[d] Consider use of myeloid growth factors before bendamustine dosage reduction.
[e] Consider discontinuing bendamustine if additional dosage reduction is required.
[f] For thrombocytopenia, a platelet count below 50 x 10^9/L should prompt bendamustine dose interruption even in the absence of clinically significant bleeding.

Refer to the prescribing information of each of the products used in combination with CALQUENCE for additional information for management of 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 32% of 1,764 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (19% of all patients, including pneumonia in 9%) *[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 2.7% 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 treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 4.4% of patients, with fatal hemorrhage occurring in 0.2% of 1,764 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 40% 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 7% of patients taking CALQUENCE without antithrombotic agents and 4% 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

CALQUENCE can cause Grade 3 or 4 cytopenias. Grade 3 or 4 cytopenias included absolute neutrophil count decreased (26%), platelets decreased (10%), hemoglobin decreased (10%), and absolute lymphocyte count decreased (10%) in patients treated with CALQUENCE alone or in combination with obinutuzumab; Grade 4 neutropenia developed in 14% *[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 18% of 1,764 patients exposed to CALQUENCE in clinical trials *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The most frequent second primary malignancy was non-melanoma skin cancer, reported in 10% of patients, followed by other solid tumors in 9% (including melanoma, lung cancer, gastrointestinal cancers, and genitourinary cancers) and hematologic malignancies (1%). Monitor patients for the development of second cancers and advise protection from sun exposure.

Cardiac Arrhythmias

Fatal and serious cardiac arrhythmias have occurred in patients treated with CALQUENCE. Grade 3 or 4 atrial fibrillation or flutter was reported in 2.6% of 1,764 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 7% of all patients *[see Adverse Reactions (6.1) in the full Prescribing Information]*. Grade 3 or higher ventricular arrhythmia events were reported in 0.6% of patients, including fatal cases in 0.3% of all patients. The risk of arrhythmias 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.

Hepatotoxicity, Including Drug-Induced Liver Injury

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), has occurred in patients treated with Bruton tyrosine kinase inhibitors, including CALQUENCE.

Evaluate bilirubin and transaminases at baseline and throughout treatment with CALQUENCE. For patients who develop abnormal liver tests after CALQUENCE, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold CALQUENCE. Upon confirmation of DILI, discontinue CALQUENCE.

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]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Hepatotoxicity, including DILI *[see Warnings and Precautions (5.6) in the full Prescribing Information]*

Clinical Trials Experience

Because 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 1,764 patients with hematologic malignancies. Treatment includes CALQUENCE monotherapy in 1,256 patients in 9 trials, and CALQUENCE combinations in 508 patients in 3 trials. Among these recipients of CALQUENCE, 88% were exposed for at least 6 months and 80% were exposed for at least one year. In this pooled safety population, adverse reactions in ≥ 30% of 1,764 patients, excluding laboratory abnormalities, were diarrhea (37%), upper respiratory tract infection (36%), headache (35%), musculoskeletal pain (33%), lower respiratory tract infection (32%), and fatigue (32%). The most common grade 3 or 4 laboratory abnormalities (≥10%) were absolute neutrophil count decreased (31%), absolute lymphocyte count decreased (23%), platelets decreased (11%), and hemoglobin decreased (10%).

Previously Untreated Mantle Cell Lymphoma

The safety data described below reflect exposure to CALQUENCE (100 mg approximately every 12 hours, with or without BR) in patients with MCL *[see Clinical Studies (14.1) in the full Prescribing Information]*.

ECHO

The safety of CALQUENCE in combination with bendamustine and rituximab (CALQUENCE plus BR) was evaluated in 297 patients with previously untreated MCL in ECHO *[see Clinical Studies (14.1) in the full Prescribing Information]*. The trial enrolled patients with previously untreated MCL, ≥ 65 years of age with no intention for transplant, total bilirubin ≤ 1.5 × ULN, AST or ALT ≤ 2.5 × ULN, and estimated creatinine clearance of > 50 mL/min. Patients received 6 cycles (as 28-day cycles) of CALQUENCE 100 mg orally twice daily (n = 297) or placebo (n = 297) in combination with bendamustine and rituximab. Patients then received CALQUENCE 100 mg orally twice daily or placebo continuously until progressive disease or unacceptable toxicity, with 12 additional dosages of rituximab every other cycle up to Cycle 30.

The median duration of treatment with CALQUENCE was 28.6 months. A total of 171 (57.6%) patients were treated with CALQUENCE for > 24 months and 122 (41.1%) patients were treated for > 36 months.

Serious adverse reactions occurred in 69% of patients who received CALQUENCE plus BR. Serious adverse reactions reported in ≥ 2% of patients were pneumonia (23%; includes COVID-19 pneumonia), COVID-19 (20%; includes COVID-19 pneumonia), pyrexia (6%), second primary malignancy (7%), rash (3.4%), febrile neutropenia (3.4%), atrial fibrillation (3%), sepsis (2.7%), and anemia (2.4%). Fatal adverse reactions that occurred within 30 days of the last study treatment were reported in 12% who received CALQUENCE plus BR including COVID-19 (6%; includes COVID-19 pneumonia), pneumonia (1%), sepsis (0.3%), second primary malignancy (0.7%), and pneumonitis (0.3%).

Adverse reactions led to permanent discontinuation of CALQUENCE in 43%, dosage interruptions in 74%, and dosage reductions in 10% of patients. Adverse reactions that resulted in dosage modification in > 10% included infections, cytopenias, rashes, and gastrointestinal toxicity. Adverse reactions which resulted in permanent discontinuation of CALQUENCE in ≥ 4% of patients included COVID-19 (includes COVID-19 pneumonia) and neutropenia.

Table 4 and Table 5 summarize select adverse reactions and laboratory abnormalities observed in patients treated in ECHO.

Table 4: Adverse Reactions* (≥ 15%) in Patients with Previously Untreated MCL Who Received CALQUENCE plus BR in ECHO

Body System Adverse Reactions*	CALQUENCE plus BR N = 297		Placebo plus BR N = 297	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash[a]	47	12	31	3
Infections				
COVID-19[b]	38	13	27	11
Upper respiratory tract infection[c]	30	0.7	29	1
Pneumonia[d]	31	17	25	14
Gastrointestinal disorders				
Diarrhea	37	3	28	2.4
Vomiting	26	0.7	14	1
Constipation	25	1	25	0.3
General disorders				
Fatigue	37	3.7	32	4.4
Pyrexia	29	2.4	24	1.3
Edema	20	1.3	19	0
Nervous system disorders				
Headache	31	1.7	14	0.7
Dizziness	18	1	17	0.3
Respiratory, thoracic and mediastinal disorders				
Cough	27	0	20	0.3
Dyspnea	17	1	11	2.7
Neoplasms				
Secondary primary malignancy[e]	19	7	15	7
Musculoskeletal and connective tissue disorders				
Arthralgia	18	0.7	16	1
Vascular disorders				
Hemorrhage[f]	20	1.7	11	3

*Excludes laboratory terms.
[a] Includes rash, dermatitis, and other related terms.
[b] Includes the following fatal adverse reactions: n=24 for COVID-19.
[c] Includes upper respiratory tract infection, sinusitis, pharyngitis, and related terms.
[d] Includes pneumonia, terms containing pneumonia, and related infections. COVID-19 pneumonia is represented under both Pneumonia and COVID-19.
[e] Includes terms related to malignant neoplasms including cutaneous neoplasms.
[f] Includes all terms containing hematoma or hemorrhage and related terms indicative of bleeding.

Clinically relevant adverse reactions in < 15% of patients receiving CALQUENCE plus BR included bruising, abdominal pain, atrial fibrillation or flutter, and tumor lysis syndrome.

Table 5: Select Laboratory Abnormalities (≥ 15%) in Patients with Previously Untreated MCL in ECHO

Laboratory Abnormality	CALQUENCE plus BR[a]		Placebo plus BR[a]	
	All grade (%)	Grade 3 or 4 (%)	All grade (%)	Grade 3 or 4 (%)
Hematologic Abnormalities				
Lymphocytes decreased	98	87	97	89
Hemoglobin decreased	80	11	65	11
Neutrophils decreased	76	56	77	51
Platelets decreased	69	18	60	16
Chemistry Abnormalities				
AST increased	53	5	50	3.4
Uric acid increased	45	45	40	40
ALT increased	44	7	41	2.4
Potassium increased	40	2	38	2.7
Creatinine increased	37	3	28	2.4
Phosphate decreased	36	4.4	30	4.7
Potassium decreased	29	7	23	6
Bilirubin increased	19	2	12	2

[a] The denominator used to calculate the rate varied between 296 and 297 based on the number of patients with a baseline value and at least one post-treatment value.

Grade 4 laboratory abnormalities in > 15% of patients treated with CALQUENCE plus BR include absolute lymphocyte count decreased (26%), absolute neutrophil count decreased (36%), and uric acid increased (17%).

Previously Treated Mantle Cell Lymphoma

ACE-LY-004

The safety data described in this section reflect exposure to CALQUENCE (100 mg approximately every 12 hours) in 124 patients with previously treated MCL in Trial LY-004 *[see Clinical Studies (14.2) in the full Prescribing Information]*. The median duration of treatment with CALQUENCE was 16.6 (range: 0.1 to 26.6) months. A total of 91 (73.4%) patients were treated with CALQUENCE for ≥ 6 months and 74 (59.7%) patients were treated for ≥ 1 year.

The most common adverse reactions (≥ 20%) of any grade were anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising. Grade 1 severity for the non-hematologic, most common events were as follows: headache (25%), diarrhea (16%), fatigue (20%), myalgia (15%), and bruising (19%). The most common Grade ≥ 3 non-hematological adverse reaction (reported in at least 2% of patients) was diarrhea.

Dose reductions and discontinuation due to any adverse reaction were reported in 1.6% and 6.5% of patients, respectively.

Tables 6 and 7 present the frequency category of adverse reactions observed in patients with MCL treated with CALQUENCE.

Table 6: Non-Hematologic Adverse Reactions in ≥ 5% (All Grades) of Patients with MCL in Trial LY-004

Body System Adverse Reactions*	CALQUENCE Monotherapy N=124	
	All Grades (%)	Grade ≥ 3 (%)
Nervous system disorders		
Headache	39	1.6
Gastrointestinal disorders		
Diarrhea	31	3.2
Nausea	19	0.8
Abdominal pain	15	1.6
Constipation	15	-
Vomiting	13	1.6
General disorders		
Fatigue	28	0.8
Musculoskeletal and connective tissue disorders		
Myalgia	21	0.8
Skin and subcutaneous tissue disorders		
Bruising[a]	21	-
Rash[b]	18	0.8

Table 6: Non-Hematologic Adverse Reactions in ≥ 5% (All Grades) of Patients with MCL in Trial LY-004 (cont'd)

Body System Adverse Reactions*	CALQUENCE Monotherapy N=124	
	All Grades (%)	Grade ≥ 3 (%)
Vascular disorders		
Hemorrhage[c]	8	0.8
Respiratory, thoracic and mediastinal disorders		
Epistaxis	6	-

* Per NCI CTCAE version 4.03.
[a] Bruising: Includes all terms containing 'bruise,' 'contusion,' 'petechiae,' or 'ecchymosis'.
[b] Rash: Includes all terms containing 'rash'.
[c] Hemorrhage: Includes all terms containing 'hemorrhage' or 'hematoma'.

Table 7: Hematologic Adverse Reactions Reported in ≥ 20% of Patients with MCL in Trial LY-004

Hematologic Adverse Reactions*	CALQUENCE Monotherapy N=124	
	All Grades (%)	Grade ≥ 3 (%)
Hemoglobin decreased	46	10
Platelets decreased	44	12
Neutrophils decreased	36	15

*Per NCI CTCAE version 4.03; based on laboratory measurements and adverse reactions.

Increases in creatinine to 1.5 to 3 times the upper limit of normal (ULN) occurred in 4.8% of patients.

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 (14.3) 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 (14.3) 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 8 and 9 present adverse reactions and laboratory abnormalities identified in the ELEVATE-TN trial.

Table 8: 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[a]	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 9: 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 (14.3) 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 10 and non-hematologic laboratory abnormalities are described in Table 11. 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 10: 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

Table 10: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE in Patients with CLL (ASCEND) (cont'd)

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 (%)
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 11: 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.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of CALQUENCE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Cardiac disorders: ventricular arrhythmias
- Hepatobiliary disorders: drug-induced liver injury

DRUG INTERACTIONS

Effect of Other Drugs on CALQUENCE

Strong CYP3A Inhibitors	
Clinical Effect	Co-administration of CALQUENCE with a strong CYP3A inhibitor increased acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	Avoid co-administration of CALQUENCE with strong CYP3A inhibitors. Alternatively, if the inhibitor will be used short-term, interrupt CALQUENCE *[see Dosage and Administration (2.2) in the full Prescribing Information]*.
Moderate CYP3A Inhibitors	
Clinical Effect	Co-administration of CALQUENCE with a moderate CYP3A inhibitor may increase acalabrutinib plasma concentration *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	Reduce the dosage of CALQUENCE when co-administered with a moderate CYP3A inhibitor *[see Dosage and Administration (2.2) in the full Prescribing Information]*.
Strong CYP3A Inducers	
Clinical Effect	Co-administration of CALQUENCE with a strong CYP3A inducer decreased acalabrutinib plasma concentration *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Decreased acalabrutinib concentrations may reduce CALQUENCE activity.
Prevention or Management	Avoid co-administration of CALQUENCE with strong CYP3A inducers. If co-administration is unavoidable, increase the dosage of CALQUENCE *[see Dosage and Administration (2.2) in the full Prescribing Information]*.

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

CLL and Previously Treated MCL

Of the 1,467 CALQUENCE-treated patients with CLL or relapsed or refractory MCL in clinical trials, 977 (67%) were 65 years of age or older, and 328 (22%) were 75 years of age or older. Among patients 65 years of age or older, 74% had Grade 3 or higher adverse reactions and 58% had serious adverse reactions. Among patients younger than age 65, 61% had Grade 3 or higher adverse reactions and 39% had serious adverse reactions. No clinically relevant differences in efficacy were observed between patients ≥ 65 years and younger.

Previously Untreated MCL

Of the 297 CALQUENCE-treated patients with previously untreated MCL, 214 (72%) were 65 to 74 years of age and 83 (28%) were 75 years of age and older. No clinically relevant differences in safety or efficacy were observed between patients ages 65 to 74 years and those who were 75 years of age and older.

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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