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A SPECIAL MEETING REVIEW EDITION

Highlights in Chronic Lymphocytic Leukemia From the 61st American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 61st ASH Meeting • December 7-10, 2019 • Orlando, Florida

Special Reporting on:

- ELEVATE TN: Phase 3 Study of Acalabrutinib Combined With Obinutuzumab or Alone vs Obinutuzumab Plus Chlorambucil in Patients With Treatment-Naive Chronic Lymphocytic Leukemia
- Treatment Patterns and Outcomes of 1205 Patients on Novel Agents in the US Veterans Health Administration System: Results From the Largest Retrospective EMR and Chart Review Study in the Real-World Setting
- Preliminary Safety and Efficacy Results From a Phase 2 Study of Acalabrutinib, Venetoclax, and Obinutuzumab in Patients With Previously Untreated Chronic Lymphocytic Leukemia
- Four-Year Analysis of the MURANO Study Confirms Sustained Benefit of Time-Limited Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia
- Treatment With the Bruton Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111) Demonstrates High Overall Response Rate and Durable Responses in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Updated Results From a Phase 1/2 Trial
- Rapid Undetectable MRD Responses in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Treated With Lisocabtagene Maraleucel (liso-cel), a CD19-Directed CAR T-Cell Product: Updated Results From TRANSCEND CLL 004, a Phase 1/2 Study Including Patients With High-Risk Disease Previously Treated With Ibrutinib
- Combined Ibrutinib and Venetoclax for Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

PLUS Meeting Abstract Summaries

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ELEVATE TN: Phase 3 Study of Acalabrutinib Combined With Obinutuzumab or Alone vs Obinutuzumab Plus Chlorambucil in Patients With Treatment-Naive Chronic Lymphocytic Leukemia

Ibrutinib is an oral Bruton tyrosine kinase (BTK) inhibitor that is approved for the treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).[1] Acalabrutinib is an irreversible BTK inhibitor that is more highly selective than ibrutinib.[2] The multicenter, open-label, phase 3 ELEVATE TN trial (ELEVATE CLL TN: Study of Obinutuzumab + Chlorambucil, Acalabrutinib [ACP-196] + Obinutuzumab, and Acalabrutinib in Subjects With Previously Untreated CLL) investigated the safety and efficacy of acalabrutinib alone or combined with obinutuzumab in treatment-naive patients with CLL.[3] The control arm was standard treatment with chlorambucil plus obinutuzumab.[3] Eligible patients were ages 65 years or older, or younger than 65 years if they had coexisting conditions, such as a Cumulative Illness Rating Scale score higher than 6 or creatinine clearance below 70 mL/min.

Patients were stratified based on chromosome 17p deletion (del[17p]), Eastern Cooperative Oncology Group (ECOG) performance status, and geographic location. They were randomly assigned into 1 of 3 treatment arms. Acalabrutinib monotherapy was administered at a dose of 100 mg, twice daily. Patients in the acalabrutinib plus obinutuzumab arm received the same dose of acalabrutinib plus 6 cycles of obinutuzumab (1000 mg on days 1, 2, 8, and 15 of cycle 2, followed by 1000 mg on day 1 of subsequent cycles). Patients in the control arm received 6 cycles of obinutuzumab (starting with cycle 1) plus chlorambucil (0.5 mg/kg on days 1 and 15 of each 28-day cycle for 6 cycles). The primary endpoint was progression-free survival (PFS) with acalabrutinib plus obinutuzumab vs chlorambucil plus obinutuzumab.

The trial enrolled 565 patients into the 3 arms. The median age of the overall study population was 70 years (range, 41-90 years). In the 3 arms, the proportion of patients ages 65 years or older ranged from 80.4% to 86.4%. More than 90% of patients had an ECOG performance status of 0 or 1. Between 44.1% and 48.6% of patients had Rai stage III/IV disease. The median time from diagnosis was 30.5 months (range, 0.4-284.5 months) in the acalabrutinib plus obinutuzumab arm, 24.4 months (range, 0.4-242.6 months) in the acalabrutinib monotherapy arm, and 30.7 months (range, 0.3-247.0 months) in the chlorambucil plus obinutuzumab arm. Across the 3 treatment arms, similar proportions of patients had high-risk features, which included unmutated immunoglobulin heavy chain (*IGHV*; 57.5%-66.5%), del(11q) (17.3%-18.6%), the *TP53* mutation (10.6%-11.9%), the complex karyotype (16.2%-18.1%), and del(17p) (8.9%-9.5%).

One patient (0.6%) in the acalabrutinib monotherapy arm and 8 patients (4.5%) in the control arm did not receive therapy. At the time of the study report, treatment was ongoing in 79.3% of patients in both the acalabrutinib arms vs 0% in the control arm. In the control arm, 77.4% of patients had completed the regimen of chlorambucil plus obinutuzumab. Rates of treatment discontinuation ranged from 18.1% in the control arm to 20.7% in the acalabrutinib/obinutuzumab arm. The most common reasons for treatment discontinuation included adverse events (AEs; 8.9% with acalabrutinib monotherapy; 11.2% with the acalabrutinib plus obinutuzumab combination; and 14.1% with chlorambucil plus obinutuzumab). The median treatment exposure was 27.7 months (range, 2.3-40.3 months) in the acalabrutinib plus obinutuzumab arm, 27.7 months (range, 0.3-40.2 months) in the acalabrutinib monotherapy arm, and 5.6 months in the control arm (range, 0.9-7.4 months).

The interim data analysis was conducted after a median follow-up

ABSTRACT SUMMARY Ibrutinib and Rituximab Provides Superior Clinical Outcome Compared to FCR in Younger Patients With Chronic Lymphocytic Leukemia: Extended Follow-Up From the E1912 Trial

The ECOG 1912 trial compared ibrutinib plus rituximab vs fludarabine, cyclophosphamide, and rituximab (FCR) in patients with treatment-naive CLL (Abstract 33). The study enrolled patients ages 70 years or younger. Patients had an ECOG performance status of 0 to 2. Three-year PFS was 89% for ibrutinib plus rituximab vs 71% for FCR (HR, 0.39; 95% CI, 0.26-0.57; *P*<.0001). The ibrutinib combination yielded a significantly improved PFS in patients with unmutated *IGHV* (*P*<.0001), but not mutated *IGHV* (*P*=.086). Three-year OS was 99% for ibrutinib plus rituximab vs 93% for FCR (HR, 0.34; 95% CI, 0.15-0.79; *P*=.009). After a median follow-up of 48 months, AEs of grade 3 or higher occurred in 70% of the ibrutinib/rituximab arm vs 80% of the FCR arm (*P*=.013). Patients in the FCR arm were more likely to experience grade 3 to 5 AEs (80.4% vs 69.6%), including febrile neutropenia (15.8% vs 2.3%) and sepsis (3.2% vs 0.6%).

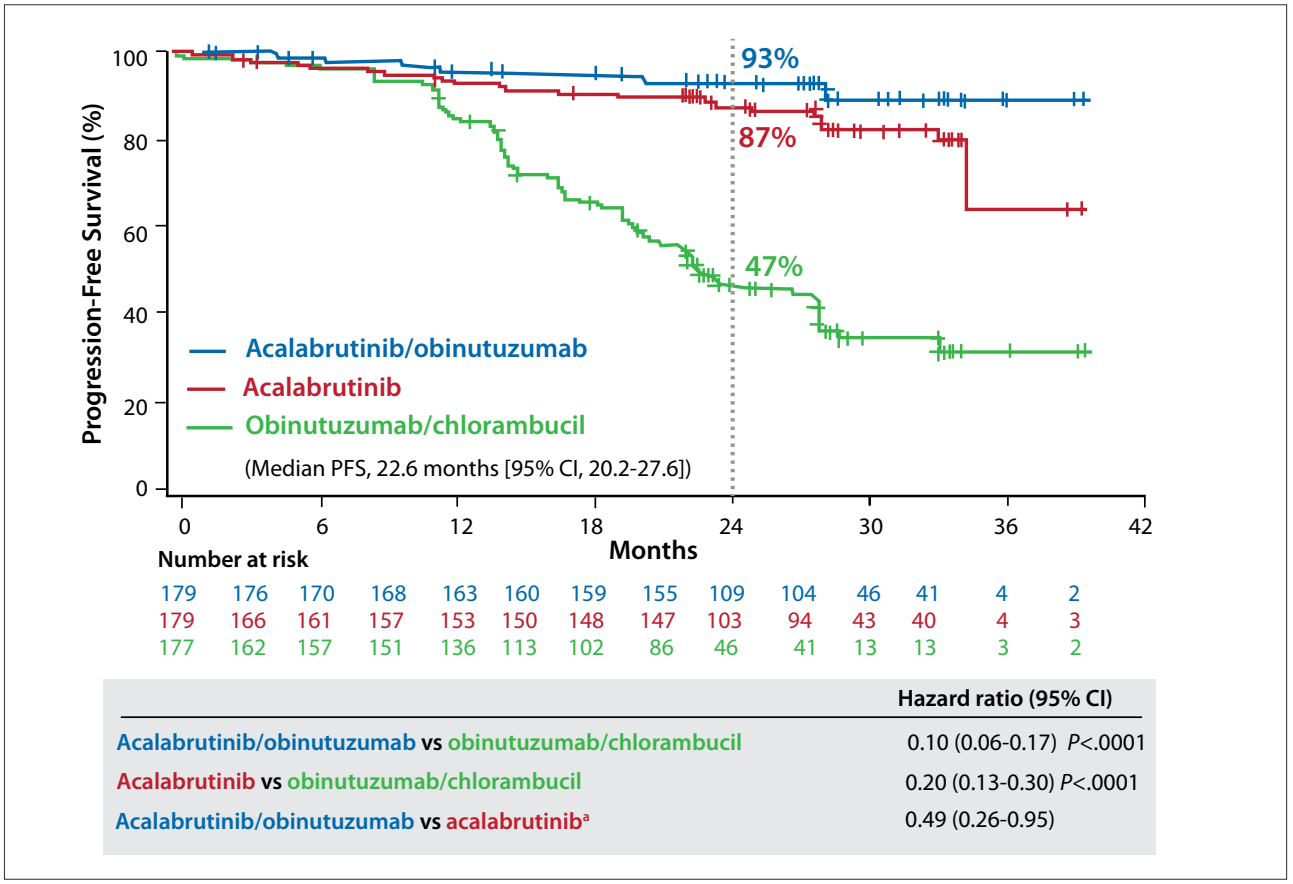

Figure 1. Interim analysis of progression-free survival according to independent review in the phase 3 ELEVATE TN trial. [a]Post hoc analysis. ELEVATE TN, Study of Obinutuzumab + Chlorambucil, Acalabrutinib (ACP-196) + Obinutuzumab, and Acalabrutinib in Subjects With Previously Untreated CLL. Adapted from Sharman JP et al. ASH abstract 31. *Blood.* 2019;134(suppl 1).[3]

of 28.3 months. The independently assessed median 2-year PFS was 93% with acalabrutinib plus obinutuzumab (hazard ratio [HR], 0.10; 95% CI, 0.06-0.17; *P*<.0001 vs the control arm), 87% with acalabrutinib monotherapy (HR, 0.20; 95% CI, 0.13-0.30; *P*<.0001 vs the control arm), and 47% with chlorambucil plus obinutuzumab (Figure 1). A post hoc exploratory analysis suggested that acalabrutinib plus obinutuzumab was superior to acalabrutinib alone (HR, 0.49; 95% CI, 0.26-0.95). In subgroup analyses, acalabrutinib, either alone or in combination with obinutuzumab, was superior to chlorambucil plus obinutuzumab regardless of age, sex, Rai disease stage, and ECOG performance status. The objective response rate (ORR) was 93.9% with the acalabrutinib combination, 85.5% with acalabrutinib monotherapy, and 78.5% in the control arm (Figure 2). The difference was statistically significant between the acalabrutinib combination vs the control (*P*<.0001), but not between acalabrutinib monotherapy vs the control (*P*<.0763). The complete response (CR) rate was 13% with acalabrutinib plus obinutuzumab, 1% with acalabrutinib monotherapy, and 5% with chlorambucil plus obinutuzumab. Median overall survival (OS) was not significantly different for the acalabrutinib combination vs standard therapy (HR, 0.47; 95% CI, 0.21-1.06; *P*=.0577) or for acalabrutinib monotherapy vs standard therapy (HR, 0.60; 95% CI, 0.28-1.27; *P*=.1556).

An AE of any grade was reported in 96.1% of the acalabrutinib plus obinutuzumab arm, 95.0% of the acalabrutinib monotherapy arm, and 98.8% of the standard treatment arm. Serious AEs occurred in 38.8%, 31.8%, and 21.9%, respectively. AEs of grade 3 or higher were observed in 70.2%, 49.7%, and 69.8%. Grade 5 AEs occurred in 2.8%, 3.9%, and 7.1%. Serious AEs were observed in 38.8% of patients in the acalabrutinib combination arm, 31.8% of patients in the acalabrutinib monotherapy arm, and 21.9% of patients in the standard treatment arm. Across the 3 arms, the most common serious AEs included pneumonia (6.7% in the acalabrutinib plus obinutuzumab arm), tumor lysis syndrome (4.7% in the chlorambucil plus obinutuzumab arm), and febrile neutropenia (4.1% in the chlorambucil plus obinutuzumab arm).

The study identified several grade 3 to 5 AEs of clinical interest for acalabrutinib. The most common

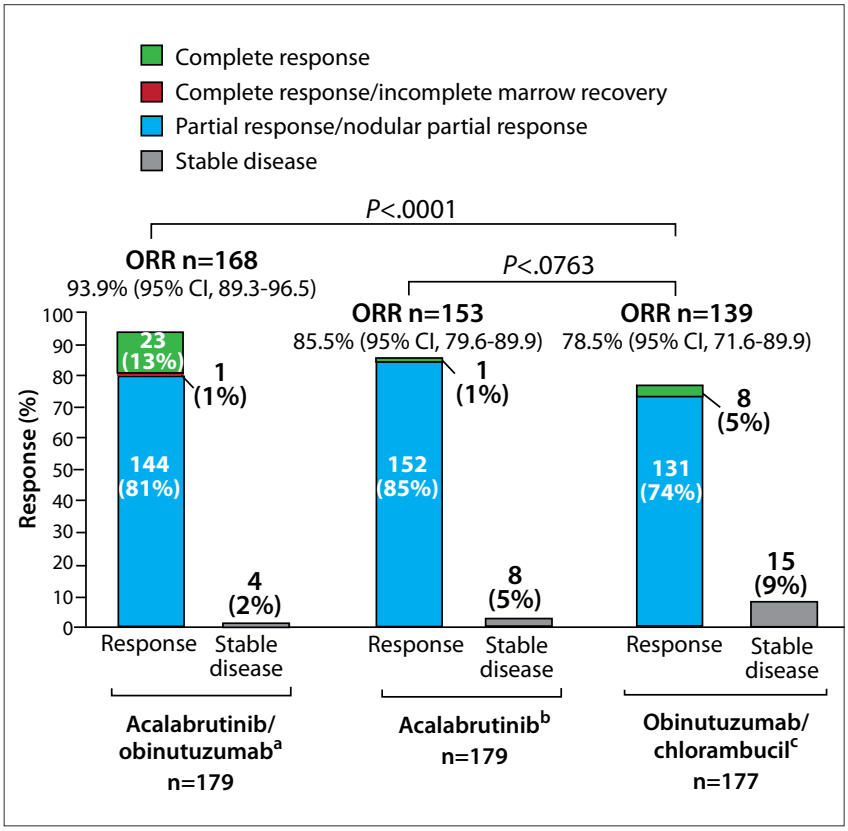

Figure 2. Response rates according to independent review in the phase 3 ELEVATE TN trial. [a]Six patients (3%) had unknown response, and 1 patient (1%) had a response of non–progressive disease, defined as lacking adequate computed tomography or magnetic resonance imaging data and not meeting criteria for progressive disease by physical examination. [b]Two patients (1%) had a partial response with lymphocytosis, 3 patients (2%) had progressive disease, 12 patients (7%) had unknown response, and response was not evaluable in 1 patient (1%). [c]Two patients (1%) had non–progressive disease, 12 patients (7%) had an unknown response, 1 patient (1%) had no evaluable disease, and response was not evaluable in 8 patients (5%). ELEVATE TN, Study of Obinutuzumab + Chlorambucil, Acalabrutinib (ACP-196) + Obinutuzumab, and Acalabrutinib in Subjects With Previously Untreated CLL; ORR, objective response rate. Adapted from Sharman JP et al. ASH abstract 31. *Blood*. 2019;134 (suppl 1).[3]

of these events were infections, which occurred in 14.0% of the monotherapy arm vs 20.8% of the combination arm; hypertension, which occurred in 2.2% vs 2.8%; and bleeding, which occurred in 1.7% of each acalabrutinib arm. Secondary primary malignancies (excluding nonmelanoma skin cancer) were reported in 1.1% of patients treated with acalabrutinib monotherapy vs 3.4% of those treated with the acalabrutinib combination. Atrial fibrillation occurred in 0.6% of each acalabrutinib arm.

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Treatment Patterns and Outcomes of 1205 Patients on Novel Agents in the US Veterans Health Administration System: Results From the Largest Retrospective EMR and Chart Review Study in the Real-World Setting

Although nearly 20,000 new cases of CLL are diagnosed every year, limited data are available regarding real-world treatment patterns with newer agents, such as ibrutinib, idelalisib, and venetoclax. The US Veterans Health Administration (VHA) conducted the CLOVER study (CLL Outcomes of Veterans in the Real World) to evaluate treatment patterns and outcomes in a large group of CLL patients who received treatment with novel agents.[1] The incidence of CLL is highest in older, white men, making the VHA database an excellent source of information on this patient population. The CLOVER study retrospectively evaluated rates of dose reduction and discontinuation, as well as the reasons for both, in real-world CLL patients who were treated with novel agents at the VHA. The study also evaluated OS and duration of therapy. Variables and outcomes were collected via a structured electronic medical records database and by chart review. Patient baseline information

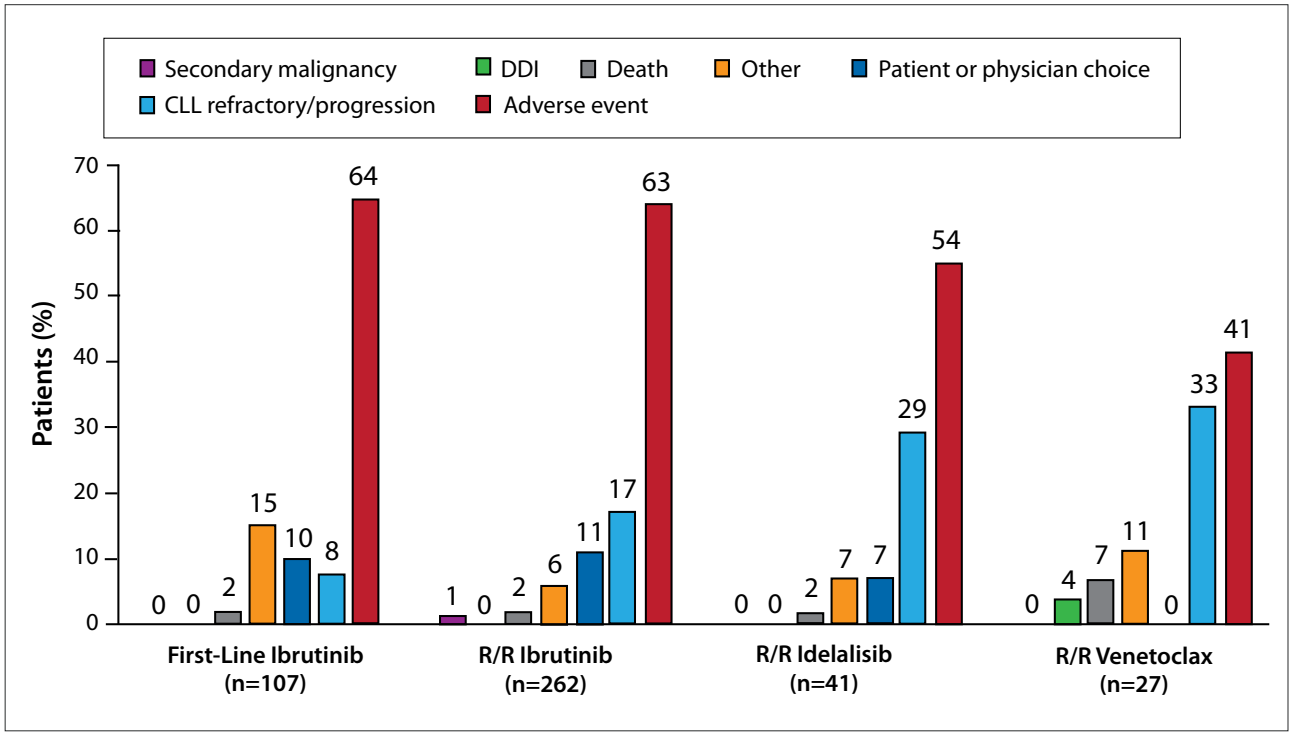

Figure 3. Reasons for treatment discontinuation among patients with chronic lymphocytic leukemia who received novel agents in a real-world analysis of data from the US Veterans Health Administration. DDI, drug-drug interaction; R/R, relapsed/refractory. Adapted from Frei CR et al. ASH abstract 795. *Blood*. 2019;134(suppl 1).[1]

was obtained from as early as October 1993 using International Classification of Diseases 9 and 10 codes. Included patients had CLL and received treatment with a novel agent from October 1, 2013 through March 31, 2018. Among 26,879 CLL patients identified, only 1366 had initiated treatment with a novel agent. The analysis excluded 161 patients. Among the 1205 patients included in the study, 1069 were treated with ibrutinib, 87 with venetoclax, and 49 with idelalisib.

Among the 1069 patients treated with ibrutinib, 328 were treatment-naive and 741 had relapsed or refractory disease. All of the patients treated with idelalisib or venetoclax had relapsed or refractory disease. Across the 4 patient cohorts, patients had a median age of 72 years (range, 45-96 years), and nearly all of the patients were male. Between 5% and 8% of patients had been exposed to Agent Orange. The most common comorbidities at baseline were coronary artery disease (18%-33%), atrial fibrillation (6%-23%), and deep vein thrombosis (3%-14%). Hypertension was present at baseline in 23% of patients who received first-line ibrutinib for CLL, whereas only 3% to 5% of patients in the other 3 cohorts had hypertension at baseline. Among patients with relapsed or refractory disease, the median number of prior CLL therapies was 2 (range, 1-14) in the ibrutinib cohort, 3 (range, 0-7) in the idelalisib cohort, and 3 (range, 1-8) in the venetoclax cohort.

Across the 4 arms, the most common reason for treatment discontinuation was AEs, ranging from 41% in the venetoclax cohort to 64% in the first-line ibrutinib cohort (Figure 3). Among patients receiving first-line ibrutinib, the most common hematologic AE that led to discontinuation was anemia (13%; 8/69). In the cohort of patients receiving ibrutinib in the second-line or later setting, the most common hematologic AEs that led to discontinuation were neutropenia (9%; 14/165) and thrombocytopenia (9%; 14/165). The most common hematologic AE that led to discontinuation was anemia (9%; 2/22) in the idelalisib cohort and neutropenia (45%; 5/11) in the venetoclax cohort. The most common nonhematologic AE that led to treatment discontinuation in the first-line ibrutinib cohort was atrial fibrillation (23%; 15/69). Among the cohorts of patients with relapsed or refractory disease, the most common nonhematologic AEs that led to treatment discontinuation were atrial fibrillation (21%; 33/165) with ibrutinib, infection (23%; 5/22) with idelalisib, and infection (18%; 2/11) with venetoclax.

Median follow-up ranged from a low of 9 months (range, 0-35 months) in the venetoclax arm to 31 months (range, 2-85 months) in patients who received ibrutinib therapy for relapsed or refractory disease. The median duration of treatment, from initiation to discontinuation, was 8 months (range, 0-49 months) in the first-line ibrutinib cohort. Among patients with relapsed

ABSTRACT SUMMARY Acalabrutinib Monotherapy in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia: 42-Month Follow-Up of a Phase 2 Study

A multicenter phase 1/2, dose-escalation study evaluated acalabrutinib monotherapy in 134 patients with relapsed or refractory CLL/SLL (Abstract 3039). Enrolled patients had received a median of 2 prior therapies (range, 1-13). Patients received acalabrutinib for a median of 41 months (range, 0.2-58 months). After May 2015, all patients received acalabrutinib (100 mg, twice daily). The ORR was 94% (95% CI, 89%-97%), including a CR rate of 4%. Similar response rates were observed across subgroups based on genetic risk factors. The estimated 45-month PFS was 62%. Overall, 44% of patients discontinued therapy. The most common reasons included progressive disease or Richter transformation and AEs. The most common AEs of grade 3 or higher were neutropenia (14%), pneumonia (11%), hypertension (7%), and anemia (7%). Thirteen cases of any-grade atrial fibrillation were observed in 10 patients.

or refractory disease, the median duration of treatment was 12 months (range, 0-81 months) with ibrutinib, 5 months (range, 0-50 months) with idelalisib, and 5 months (range, 0-22 months) with venetoclax. Treatment discontinuation rates were higher in the VHA real-world study compared with outcomes from patients in clinical trials.[2-5]

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Preliminary Safety and Efficacy Results From a Phase 2 Study of Acalabrutinib, Venetoclax, and Obinutuzumab in Patients With Previously Untreated Chronic Lymphocytic Leukemia

The phase 3 CLL14 study (A Study to Compare the Efficacy and Safety of Obinutuzumab + Venetoclax [GDC-0199] Versus Obinutuzumab + Chlorambucil in Participants With Chronic Lymphocytic Leukemia) demonstrated that fixed-duration therapy with venetoclax plus obinutuzumab yielded a longer PFS compared with chlorambucil plus obinutuzumab in 432 CLL patients with comorbidities.[1] After a median follow-up of 28.1 months, estimated 2-year PFS was 88.2% with obinutuzumab plus venetoclax vs 64.1% with standard treatment (HR, 0.35; 95% CI, 0.23-0.53; *P*<.001). A phase 1b study evaluated the combination of ibrutinib plus venetoclax and obinutuzumab in 12 patients with relapsed or refractory CLL.[2] The study yielded an ORR of 92% (95% CI, 62%-100%), with a 42% CR/incomplete CR rate. Six patients had no detectable CLL cells in both the blood and bone marrow at the end of treatment. Infusion reactions were reported in 83.3%. Grade 3/4 AEs included infusion-related reaction (8.3%), neutropenia (33.3%), and hypertension (25%). The combination of acalabrutinib plus obinutuzumab demonstrated efficacy with acceptable tolerability in the first-line setting in the ELEVATE TN trial.[3]

An open-label, single-arm, investigator-initiated, phase 2 trial evaluated the combination of acalabrutinib, venetoclax, and obinutuzumab as first-line treatment.[4] The regimen was administered in a time-limited strategy. Eligible patients had a confirmed diagnosis of treatment-naive CLL/SLL requiring treatment and a maximum ECOG performance status of 2. Acalabrutinib and obinutuzumab were administered at standard doses, and each cycle was 28 days. Patients first received a single cycle of acalabrutinib, with obinutuzumab added in cycle 2. On day 1 of cycle 4, venetoclax was added and escalated from 20 mg (cycle 4, day 1) to 400 mg, for a total of 4 cycles of triple-combination therapy. After 6 months of obinutuzumab, patients could continue to receive acalabrutinib plus venetoclax through cycle 24. However, patients with a CR and undetectable minimal residual disease (MRD) in the bone marrow were allowed to stop therapy after cycle 15. The primary endpoint was the rate of CR with undetectable MRD in the bone marrow.

The 37 enrolled patients were a median age of 63 years (range, 41-78 years), and 27% were female. All of the

patients had an ECOG performance status of 0 or 1, and 54.1% had Rai stage III/IV disease. Genomic aberrations of interest included unmutated *IGHV* (62.2%), *TP53* aberrancy (27.0%), del(11q) (29.7%), and complex karyotype (19.0%).

After 8 treatment cycles, the ORR was 100%, with a CR/incomplete CR rate of 25% (8/32). After 16 treatment cycles, the CR/incomplete CR rate was still 25% (2/8; Figure 4). Rates of undetectable MRD in the bone marrow increased over time, from 3.7% (1/27) on day 1 of cycle 4, to 48.3% (15/31) on day 1 of cycle 8, to 75.0% (6/8) on day 1 of cycle 16 (Figure 5). No significant differences in ORR or undetectable MRD rate were observed between patients with vs without mutated *IGHV*. Among the patients with *TP53* aberrancy, the response rate at cycle 8 included 67% (6/9) PRs and 33% (3/9) CRs. The rate of undetectable MRD at cycle 8 was 33% (3/9) in the bone marrow and 78% (7/9) in the blood.

After a median follow-up of 11 cycles (range, 6-16 cycles), the most common nonhematologic toxicities of any grade were fatigue (84%), headache (76%), and bruising (46%). The most common grade 3/4 toxicities were hematologic. They included neutropenia (32%), thrombocytopenia (11%), and anemia (8%). In addition to 3 reports of grade 4 neutropenia, other serious AEs included 2 cases of grade 3 laboratory tumor lysis syndrome, 1 case of grade 4 hyperkalemia, and 1 case of grade 3 elevated cardiac troponin. By starting treatment with 3 cycles of lead-in therapy with acalabrutinib and obinutuzumab, the proportion of patients with a high risk of tumor lysis syndrome was reduced from 30% at baseline to 2% at the time of venetoclax introduction.

AEs of special interest included 7 cases of grade 1/2 infusion-related reactions, plus 1 grade 3 event; 2 cases of grade 1/2 hypertension; and 1 case of grade 3 atrial fibrillation (which developed along with pericarditis

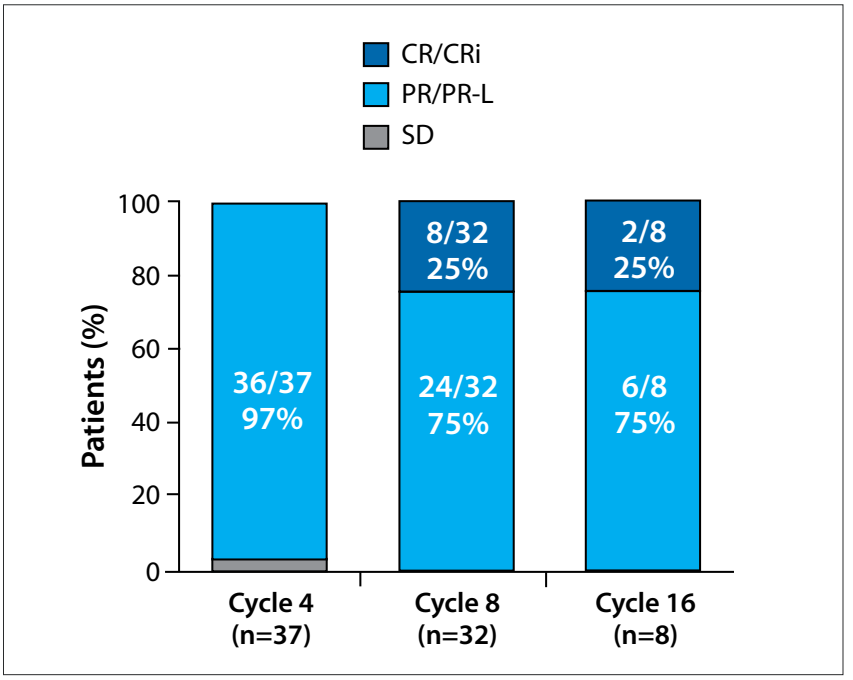

Figure 4. Efficacy results from a phase 2 study of acalabrutinib, venetoclax, and obinutuzumab in patients with previously untreated chronic lymphocytic leukemia. CR, complete response; CRi, incomplete response; PR, partial response; PR-L, partial response with lymphocytosis. Adapted from Lampson BL et al. ASH abstract 32. *Blood.* 2019;134(suppl 1).[4]

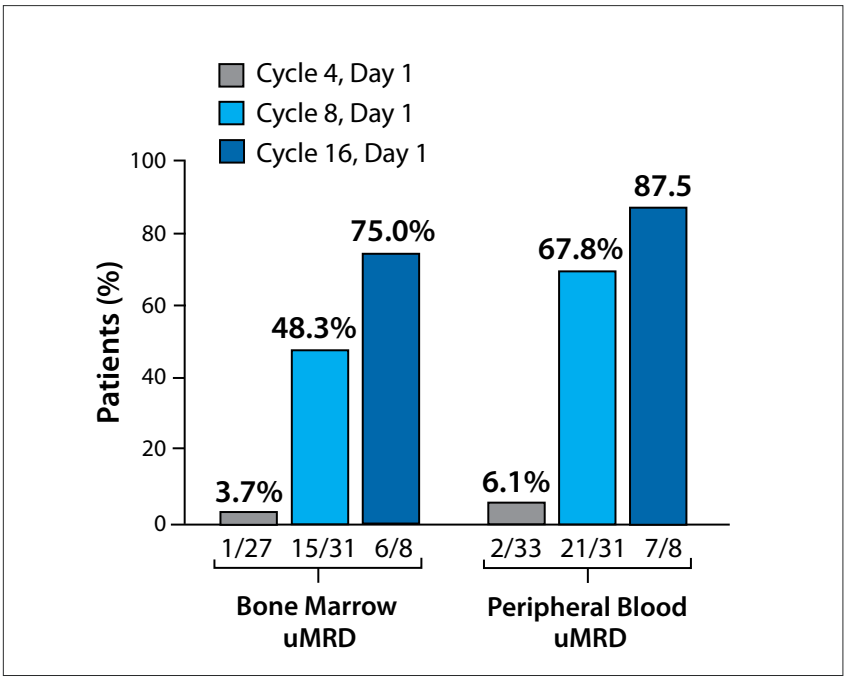

Figure 5. Rates of uMRD in a phase 2 study of acalabrutinib, venetoclax, and obinutuzumab in patients with previously untreated chronic lymphocytic leukemia. uMRD, undetectable minimal residual disease. Adapted from Lampson BL et al. ASH abstract 32. *Blood.* 2019;134(suppl 1).[4]

during cycle 9). In 1 patient, headaches required 2 dose reductions of acalabrutinib to 100 mg, with subsequent reescalation to the full dose. Another patient required a dose reduction of venetoclax to 300 mg daily owing to grade 4 neutropenia, despite growth factor support. One patient discontinued therapy. This patient, at baseline, had erosive gastritis, duodenitis, and symptomatic splenomegaly, and developed worsening of gastrointestinal symptoms during the study. Although this patient had a partial response (PR) at restaging on day 1 of cycle 4, study therapy was stopped during cycle 5.

An expansion cohort will evaluate the combination of acalabrutinib, obinutuzumab, and venetoclax in patients with *TP53* aberrancy. A phase 3 trial will compare the 3-agent combination vs acalabrutinib plus venetoclax or chemoimmunotherapy in approximately 780 patients with treatment-naive CLL.[5]

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Four-Year Analysis of the MURANO Study Confirms Sustained Benefit of Time-Limited Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia

The phase 3 MURANO trial (A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia) evaluated venetoclax plus rituximab vs bendamustine plus rituximab in patients with relapsed or refractory CLL.[1-3] Patients were stratified based on the presence of del(17p), response to prior therapy, and geographic region, and then randomly assigned to treatment. Patients initially received venetoclax (400 mg daily) plus rituximab (375 mg/m^2 on day 1 of cycle 1, then 500 mg/m^2 on day 1 of cycles 2-6) or bendamustine (70 mg/m^2 on days 1 and 2 of cycles 1-6) plus the same regimen of rituximab. After 6 cycles of combination treatment, patients in the venetoclax arm continued to receive daily venetoclax until a maximum of 2 years from day 1 of cycle 1. The primary endpoint was investigator-assessed PFS.

Baseline characteristics were well balanced between the 2 arms. Among the 389 patients randomly assigned to treatment, the median age was 65.5 years (range, 22-85 years). Two-thirds of patients had a lymphocyte count of at least 25 × 10^9/L. Forty-two percent had del(17p) or a deleterious mutation in the *TP53* gene. Twelve percent of patients in the venetoclax arm and 18% in the bendamustine arm had received 3 or more prior therapies. After a median follow-up of 36 months, treatment with venetoclax plus rituximab was superior to bendamustine plus rituximab, based on median PFS (HR, 0.16; 95% CI, 0.12-0.23; *P*<.001) and median OS (HR, 0.50; 95% CI, 0.30-0.85; *P*=.0093). Estimated 3-year PFS was 71.4% with venetoclax plus rituximab vs 15.2% with venetoclax plus bendamustine. The 3-year OS estimates were 87.9% vs 79.5%, respectively.

After a median follow-up of 48 months, 30 patients in the venetoclax combination arm and 63 in the bendamustine combination arm had discontinued treatment.[3] Among 194 patients randomly assigned to the venetoclax plus rituximab arm, 174 (90%) completed all 6 cycles of combination therapy, and 130 (67%) completed 2 years of venetoclax monotherapy without progressive disease. Among 195 patients assigned to bendamustine plus rituximab, 154 (79%) completed 6 cycles of treatment. Subsequent treatment after disease progression was reported in 42 patients in the venetoclax arm vs 103 patients in the bendamustine arm.

The 48-month analysis continued to show a benefit with venetoclax plus rituximab vs bendamustine plus rituximab.[3] Four-year PFS was 57.3% vs 4.6% (HR, 0.19; 95% CI, 0.14-0.25; *P*<.0001). In the venetoclax/rituximab arm, 83 patients (64%) had undetectable MRD (<10^{-4}) in the peripheral blood after completing 6 cycles of combination therapy plus 24 months of venetoclax monotherapy. Among the 130 patients who completed 2 years of venetoclax, 35 progression events had occurred at a median of 22 months after cessation of all therapy. Median PFS was longest in patients who had undetectable MRD at the end of treatment (24-month median PFS, 83.9%; 95% CI, 72.9%-94.9%).

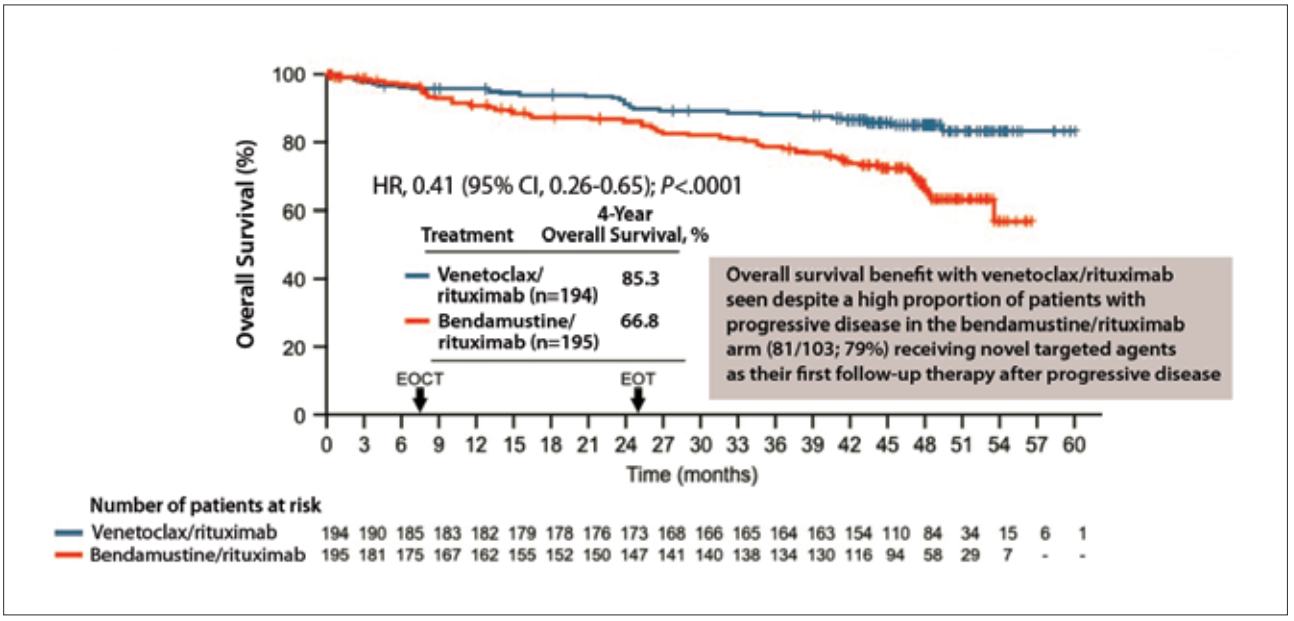

Figure 6. Overall survival in a 4-year analysis of patients in the MURANO trial. MURANO, A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia. HR, hazard ratio; EOCT, end of combination treatment; EOT, end of treatment; OS, overall survival. Adapted from Seymour JF et al. ASH abstract 355. *Blood*. 2019;134(suppl 1).[3]

Among the 14 patients who had an MRD level higher than 10^{-2}, most experienced an initial decrease in the proportion of CLL cells in the peripheral blood, followed by an increase from approximately 8 months until the end of treatment.

The 48-month analysis demonstrated a significant improvement in OS with venetoclax plus rituximab (85.3% vs 66.8%; HR, 0.41; 95% CI, 0.26-0.65; *P*<.0001; Figure 6), despite the fact that 81 patients (79%) with progressive disease in the bendamustine plus rituximab arm received treatment with a novel targeted agent as their first follow-up therapy after progression. After subsequent therapy, the ORR was 77.3% in the venetoclax arm vs 64.3% in the bendamustine arm. Among 10 patients in the venetoclax plus rituximab arm who subsequently developed progressive disease and received treatment with ibrutinib, 9 achieved a PR and 1 a CR.

No new safety signals emerged during the extended follow-up. There were no reports of new serious AEs that were related to study treatment.

ABSTRACT SUMMARY Efficacy and Safety of Zanubrutinib in Patients With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma With Del(17p): Initial Results From Arm C of the SEQUOIA (BGB-3111-304) Trial

Patients enrolled into arm C of the SEQUOIA trial (A Study Comparing BGB-3111 With Bendamustine Plus Rituximab in Patients With Previously Untreated CLL or SLL) had treatment-naive CLL, were ages 65 years or older or were unsuitable for treatment with FCR, and had del(17p) disease. The patients (n=109) received treatment with single-agent zanubrutinib (160 mg, twice daily) until disease progression, unacceptable toxicity, or the end of the study (Abstract 499). The ORR was 92.7% (95% CI, 86.0%-96.8%), including a CR rate of 1.9%. Four patients had progressive disease, including 1 patient with Richter transformation. After a median follow-up of 10.0 months (range, 5.0-18.1 months), 36.7% of patients had experienced an AE of grade 3 or higher. Serious AEs were observed in 23.9% of patients. One patient (0.9%) discontinued treatment owing to an AE, and 1 patient (0.9%) experienced a grade 5 AE.

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Treatment With the Bruton Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111) Demonstrates High Overall Response Rate and Durable Responses in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Updated Results From a Phase 1/2 Trial

Zanubrutinib is a next-generation BTK inhibitor designed to maximize binding to BTK while minimizing off-target activity. The multicenter, open-label, phase 1/2 AU-003 trial (Study of the Safety and Pharmacokinetics of BGB-3111 in Subjects With B-Cell Lymphoid Malignancies) investigated the safety, efficacy, and pharmacokinetics of zanubrutinib in patients with B-cell malignancies.[1,2] Patients were enrolled into disease-specific expansion cohorts. The doses of zanubrutinib ranged from 40 mg once daily to 160 mg twice daily or 360 mg once daily until unacceptable toxicity or disease progression. No dose-limiting toxicities occurred during dose escalation. BTK occupancy was 89% with the dose of 160 mg twice daily vs 50% with 360 mg once daily (P=.0342). After a median follow-up of 13.7 months, a preliminary analysis showed that zanubrutinib was associated with acceptable toxicity and promising efficacy.[2]

The AU-003 study included 123 patients with CLL/SLL and no prior exposure to BTK inhibitor therapy.[1] Among these patients, 101 had relapsed or refractory disease and 22 were treatment-naive. The patients were a median age of 67 years (range, 24-87 years), and three-fourths were male. Five patients (4.1%) had SLL. Genetic risk factors included unmutated *IGHV* (68.3%), *TP53* mutation (31.0%), del(11q) (23.5%), and del(17p) (16.2%). Bulky disease (>5 cm) was noted in 38.2% of patients. The median duration of follow-up was 29.5 months (range, 3.7-52.0 months), and the median duration of treatment was 25.8 months (range, 1.6-52.0 months). Ninety-eight patients remained on study treatment at the time of the analysis.

Based on investigator assessment, the ORR in the overall study population was 95.9%, including CRs in 15.4% and incomplete CRs in 0.8%. At 12 months, after a median follow-up of 31.2 months (range, 9.4-43.5 months), 97.2% of patients remained in response. Among 16 patients with del(17p), the ORR was 93.8%, including 1 patient (6.3%) with a CR. For PFS, the median follow-up was 32.2 months for treatment-naive patients and 23.1 months for those with relapsed or refractory disease. In the treatment-naive cohort, PFS rates were 95% at both 12 and 24 months. In the relapsed/refractory cohort, PFS rates were 97% at 12 months and 91% at 24 months. The best responses over time for the relapsed/refractory cohort are shown in Figure 7.

AEs of grade 3 or higher were observed in 61.8% of patients. Serious AEs occurred in 47.2% of patients. Five AEs (4.1%) required treatment discontinuation, and 1 AE (0.8%) led to death. The most common AEs of any grade included bruising, diarrhea, and minor bleeding. The most common AEs of grade 3 or higher were neutropenia, pneumonia, and anemia. The rate of grade 3 or higher atrial fibrillation was 1.6%. Most AEs of interest decreased in frequency after the first 12 months of treatment, with the exception of grade 3 or higher infection. The most common reason for treatment discontinuation was progressive disease (12%).

A randomized registration trial is comparing zanubrutinib vs ibrutinib in patients with relapsed or refractory CLL/SLL.[3]

ABSTRACT SUMMARY Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Results From the MRD Cohort of the Phase 2 CAPTIVATE Study

The phase 2 CAPTIVATE trial (Ibrutinib Plus Venetoclax in Subjects With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma) evaluated ibrutinib plus venetoclax in 164 treatment-naive CLL/SLL patients (Abstract 35). During the nonrandomized portion of the trial, patients received 3 cycles of ibrutinib monotherapy followed by 12 cycles of ibrutinib plus venetoclax. Thirty-two percent of patients had Rai stage III/IV disease, 59% had unmutated *IGHV*, and 20% had del(17p) or the *TP53* mutation. Ninety percent of patients completed all 15 treatment cycles, and 5% of patients discontinued all study treatment. Rates of undetectable MRD were 75% in the peripheral blood (122/163) and 72% in the bone marrow (112/155). High rates of undetectable MRD were sustained over time and observed across subgroups. The most common grade 3/4 AEs were neutropenia (35%), hypertension (7%), thrombocytopenia (5%), and diarrhea (5%). Treatment-related serious AEs were observed in 11% of patients. No patient developed clinical tumor lysis syndrome. After the nonrandomized portion of the trial, patients will receive further treatment based on MRD levels.

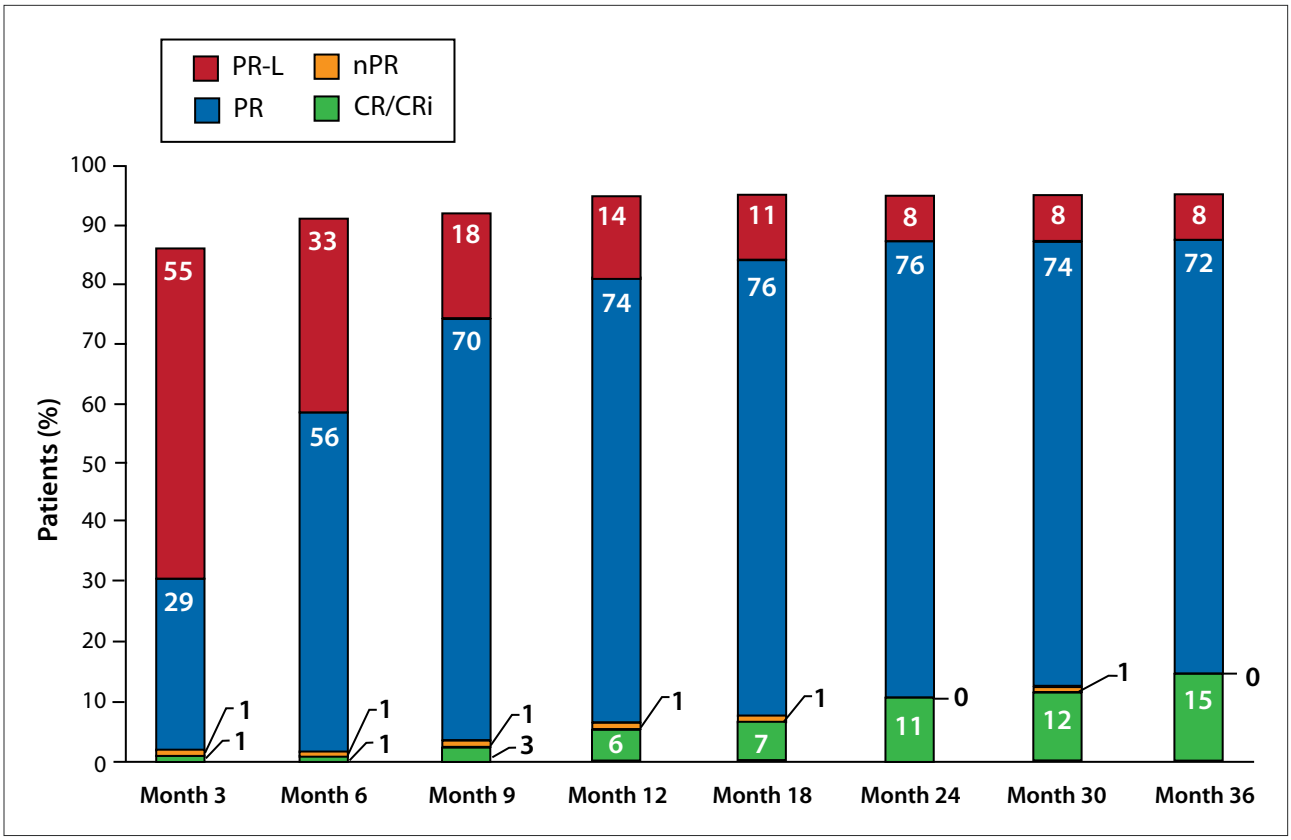

Figure 7. Best responses over time among relapsed/refractory patients with chronic lymphocytic leukemia or small lymphocytic lymphoma treated with zanubrutinib in a phase 1/2 trial. CR, complete response; iCR, incomplete response; nPR, near partial response; PR, partial response; PR-L, partial response with lymphocytosis. Adapted from Cull G et al. ASH abstract 500. *Blood*. 2019;134(suppl 1).[1]

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Rapid Undetectable MRD Responses in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Treated With Lisocabtagene Maraleucel (liso-cel), a CD19-Directed CAR T-Cell Product: Updated Results From TRANSCEND CLL 004, a Phase 1/2 Study Including Patients With High-Risk Disease Previously Treated With Ibrutinib

The phase 1/2 TRANSCEND CLL 004 trial (Study Evaluating Safety and Efficacy of JCAR017 in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia [CLL] or Small Lymphocytic Lymphoma [SLL]) evaluated lisocabtagene maraleucel (JCAR017) in heavily pretreated CLL patients, including those with an inadequate response to both a BTK inhibitor and venetoclax.[1] Lisocabtagene maraleucel is a CD19-directed chimeric antigen receptor (CAR) T-cell product that uses a defined composition of CD8- and CD4-positive T cells, with the goal of administering equal doses of both T-cell classes.

The TRANSCEND CLL 004 study included patients with relapsed or refractory CLL/SLL who had an inadequate response to BTK inhibitor therapy or were ineligible for this treatment. Eligibility criteria required that patients with high-risk disease had an inadequate response to at least 2 prior therapies, and patients with standard-risk disease had received at least 3 prior therapies. All patients had an ECOG performance status of 0 or 1. After leukapheresis, the presence of measurable disease was reconfirmed. Bridging therapy was allowed prior to lymphodepletion, which was performed by means of a 3-day regimen of fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2). Lisocabtagene maraleucel was administered in 2 dose levels: 50 × 10^6 CAR T cells (dose level 1) and 100 × 10^6 CAR T cells (dose level 2).

Among 23 evaluable patients, 9 received lisocabtagene maraleucel at 50 × 10^6 CAR T cells and 14 received lisocabtagene maraleucel at 100 × 10^6 CAR T cells. After a median follow-up of 11 months, the ORR was 81.5% (18/22), including a CR/incomplete CR rate of 45.5% (Figure 8). Among the 9 patients previously treated with a BTK inhibitor and venetoclax, the ORR was 89% (8/9), including a CR/incomplete CR rate of 67%. The rate of undetectable MRD (<10^{-4}) was 75% (15/20) in the blood and 65% (13/20) in the bone marrow. In the subgroup of patients who had failed a BTK inhibitor and venetoclax, the rate of undetectable MRD was 87.5% (7/8) in the blood and 75% (6/8) in the bone marrow. Sixty-eight percent (15/22) of patients had a response by day 30. In 27% of patients (6/22), responses deepened over time.

Among 12 patients who had a PR or CR at 6 months, 10 (83%) remained in response at 9 months, and 8 patients were in response for at least 12 months. Eighty percent (12/15) of patients who achieved undetectable MRD in the blood maintained their response, and all cases of progressive disease were associated with Richter transformation.

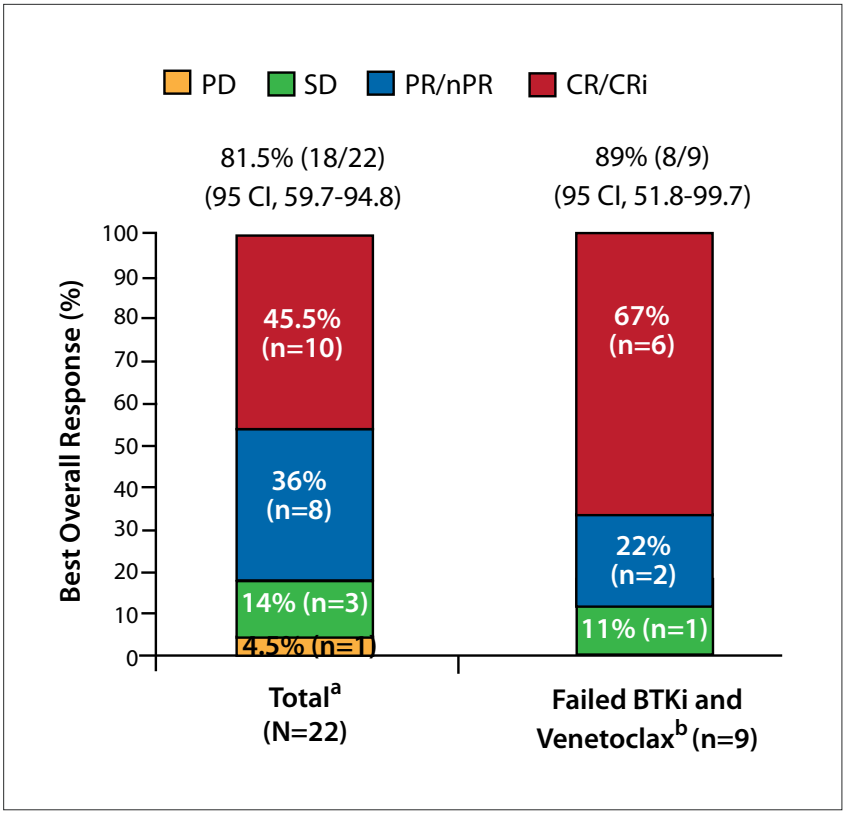

Figure 8. Responses to lisocabtagene maraleucel in the phase 1/2 TRANSCEND CLL 004 trial. [a]Evaluable for response was defined as having a pretreatment assessment and ≥1 postbaseline assessment. One patient was not evaluable for response. [b]Failure of venetoclax was defined as discontinuation owing to progressive disease or less than progressive disease after ≥3 months of therapy. BTKi, Bruton tyrosine kinase inhibitor; CR, complete response; iCR, incomplete response; PD, progressive disease; PR, partial response; SD, stable disease; TRANSCEND CLL 004, Study Evaluating Safety and Efficacy of JCAR017 in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia [CLL] or Small Lymphocytic Lymphoma [SLL]). Adapted from Siddiqi T. ASH abstract 503. *Blood*. 2019;134(suppl 1).[1]

The most common grade 3/4 treatment-emergent AEs were anemia (78%), thrombocytopenia (70%), and neutropenia (56.5%). Dose-limiting toxicities were observed in 2 patients who received the lisocabtagene maraleucel infusion at 100 × 10^6 CAR T cells, and both cases resolved. Among the 23 patients, 74% experienced cytokine release syndrome of any grade, including 2 patients (9%) who developed grade 3 cytokine release syndrome. Neurologic events of any grade were reported in 39% of patients, including 5 patients (22%) with neurologic events of grade 3 or higher.

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Combined Ibrutinib and Venetoclax for Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Two phase 2 studies evaluated ibrutinib plus venetoclax in patients with either treatment-naive or relapsed/refractory CLL/SLL.[1,2] In the treatment-naive study, patients had at least 1 high-risk feature: del(17p) or mutated *TP53*; del(11q); unmutated *IGHV*; or older age (≥65 years). Patients initially received 3 cycles of ibrutinib at 420 mg daily. Starting with cycle 4, venetoclax was initiated at 20 mg daily, with escalation to 400 mg daily, for a total of 24 cycles of combination treatment. Patients with detectable MRD in the bone marrow after 24 cycles of combination treatment could continue with ibrutinib monotherapy until disease progression. Eighty patients were enrolled. Their median age was 65 years. Five patients left the study during the first 3 cycles of ibrutinib monotherapy, and 75 initiated combination therapy. The median follow-up was 27 months.

The rate of undetectable MRD ($<10^{-4}$) in the bone marrow was 16% (12/74) after 3 months of combination therapy and increased over time to 75% after 24 months of combination therapy (37/49). High rates of undetectable MRD in the bone marrow were observed across all patient subgroups based on risk factors. Bone marrow MRD continued to improve from 12 months through 24 months.

Five patients left the study during the first 3 cycles of ibrutinib monotherapy, and another 9 patients withdrew while receiving combination therapy. No patient developed CLL progression. Two patients developed Richter transformation, and 3 patients died. Fifty-one percent of patients developed grade 3/4 neutropenia, and 24% required administration of granulocyte colony–stimulating factor. Nineteen percent of patients developed an infection of grade 3 or higher. Four patients (5%) developed neutropenic fever. Dose reductions of ibrutinib or venetoclax were required in 52% and 29% of patients, respectively.

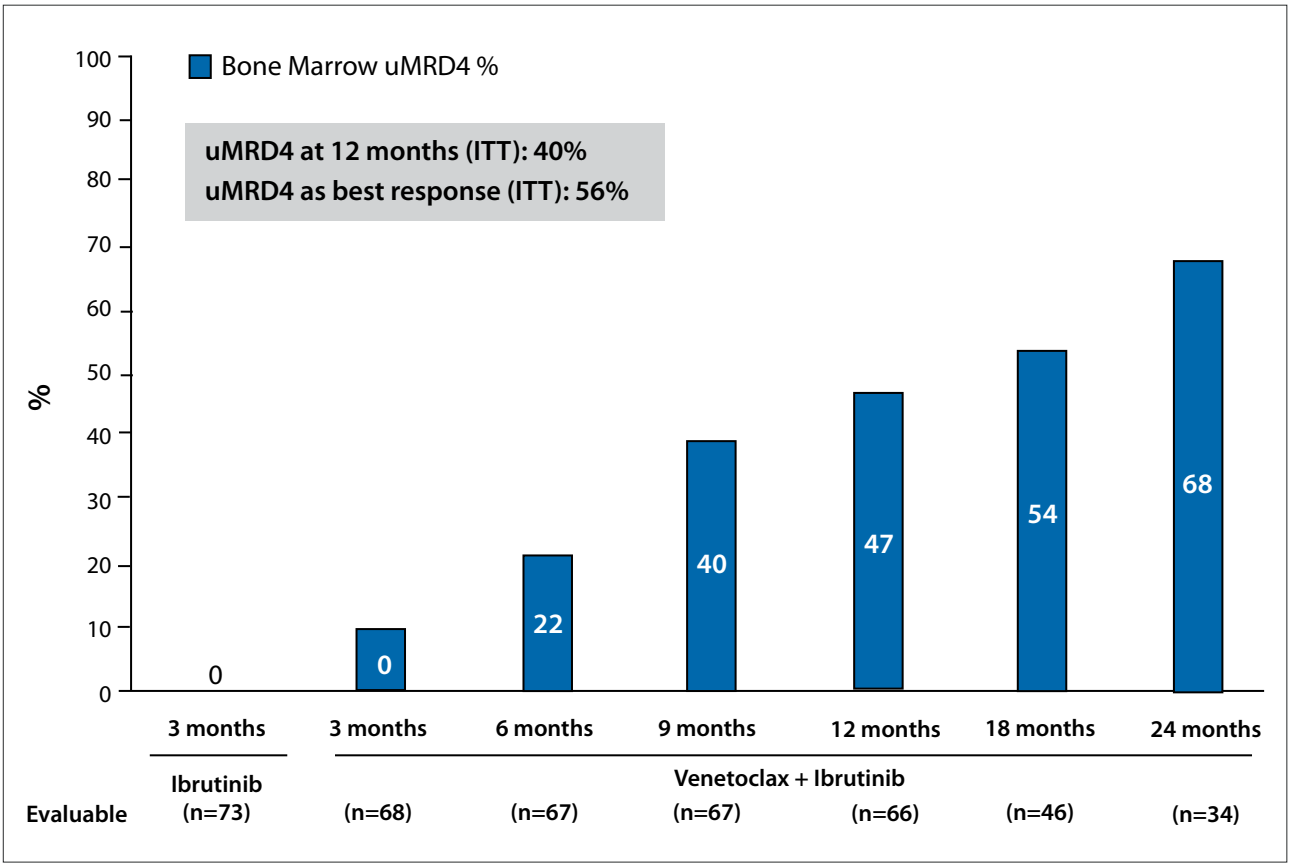

Figure 9. Rate of uMRD ($<10^{-4}$) in the bone marrow in a phase 2 study evaluating ibrutinib plus venetoclax in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. ITT, intention-to-treat; uMRD, undetectable minimal residual disease. Adapted from Jain N et al. ASH abstract 359. *Blood*. 2019;134(suppl 1).[2]

The study of relapsed or refractory patients followed the same treatment protocol. Among 80 patients enrolled, 1 was reclassified with splenic marginal zone lymphoma and excluded from further analyses. Five patients left the study during the first 3 cycles of ibrutinib monotherapy, and 74 patients began combination therapy. Median follow-up was 27 months. Patients were a median age of 61 years. The median number of prior therapies was 1 (range, 1-4), and 85% of patients had unmutated *IGHV*.

In the intention-to-treat population, the rate of undetectable MRD ($<10^{-4}$) in the bone marrow was 40% at 9 months of treatment with the combination (Figure 9). After 3 months of combination treatment, the rate of undetectable MRD in the bone marrow was 10% (7/68), which increased over time to 68% (23/34) after 24 months of combination treatment. Undetectable MRD was observed across all patient subgroups. Five patients left the study during the first 3 cycles of ibrutinib monotherapy. An additional 7 patients left during combination therapy, and 4 left after completing all cycles of combination therapy, including 2 who developed CLL progression.

AEs of interest included grade 3/4 neutropenia, reported in 43%, atrial fibrillation in 8%, and grade 3/4 thrombocytopenia in 1%. Dose reductions of ibrutinib or venetoclax were required in 57% and 35% of patients, respectively.

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Highlights in Chronic Lymphocytic Leukemia From the 61st American Society of Hematology Annual Meeting and Exposition: Commentary

Farrukh T. Awan, MD

Many presentations at the 61st American Society of Hematology annual meeting provided important insights into the management of patients with chronic lymphocytic leukemia (CLL). Studies provided new data regarding treatments such as acalabrutinib, venetoclax, ibrutinib, and zanubrutinib. In addition, multiple studies evaluating real-world management and outcomes of CLL patients were presented, including an analysis from the US Veterans Heath Administration (VHA) system.

The ELEVATE Study of Acalabrutinib

The ELEVATE trial (Study of Obinutuzumab + Chlorambucil, Acalabrutinib [ACP-196] + Obinutuzumab, and Acalabrutinib in Subjects With Previously Untreated CLL) compared acalabrutinib alone or with obinutuzumab vs chlorambucil plus obinutuzumab in patients with treatment-naive CLL who were older than 65 years or had comorbidities.[1] Obinutuzumab plus chlorambucil is an approved regimen for patients who are not candidates for more intensive chemoimmunotherapy-based regimens. The study population was similar to that enrolled in the phase 3 CLL11 trial, which examined obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.[2] Historically, the addition of a CD20 antibody to Bruton tyrosine kinase (BTK) inhibitors has not necessarily improved progression-free survival.[3,4] Nevertheless, the ELEVATE study evaluated whether the addition of the CD20 antibody obinutuzumab to acalabrutinib would improve outcomes.

Obinutuzumab is associated with a significant rate of infusion reactions when administered as monotherapy.[5] The ELEVATE trial also evaluated whether the rate of infusion reactions would be decreased if the BTK inhibitor acalabrutinib was administered before obinutuzumab, as has been seen in other studies.[6] The trial design designated that acalabrutinib was administered first, and then obinutuzumab was added later in the combination arm.

This large trial randomly assigned 535 patients to treatment: 179 to the acalabrutinib-only arm, 179 to the acalabrutinib-plus-obinutuzumab arm, and 177 to the obinutuzumab-plus-chlorambucil arm. Most of the patients were elderly, with a median age of approximately 70 years. At a median follow-up of approximately 28 months, progression-free survival was significantly improved with acalabrutinib plus obinutuzumab vs the control arm of obinutuzumab plus chlorambucil (93% vs 47%; $P<.0001$). As expected, the risk of infusion reactions was decreased by starting the BTK inhibitor prior to obinutuzumab. The rate of all-grade infusion-related reactions was 13.5% in patients treated with acalabrutinib plus obinutuzumab vs 39.6% in patients treated with obinutuzumab plus chlorambucil.

An important aspect to this study was whether the addition of obinutuzumab to acalabrutinib would improve outcomes as compared with acalabrutinib alone. There was a trend toward slightly better progression-free survival with the addition of obinutuzumab to

acalabrutinib (93% vs 87%), without a significant increase in toxicities, although the study was not powered to evaluate this endpoint. Historically, when ibrutinib was combined with the CD20 antibody rituximab, there was no significant difference in progression-free survival vs ibrutinib alone.[4] Therefore, this study provided some evidence for an improved outcome when these drug classes were combined.

No significant differences in overall survival were observed between acalabrutinib plus obinutuzumab vs obinutuzumab plus chlorambucil (hazard ratio, 0.47; 95% CI, 0.21-1.06; *P*=.0577). However, follow-up was short, and it is expected that survival would be better in the BTK inhibitor arm, as shown in previous studies of ibrutinib.[7] Longer follow-up is also needed to identify a survival difference between acalabrutinib plus obinutuzumab vs acalabrutinib alone.

Another important observation concerns the risks of bleeding, hypertension, and atrial fibrillation that have been seen with ibrutinib. In this trial, the incidence of all-grade atrial fibrillation was relatively low with acalabrutinib, at 3.4% in the combination arm and 3.9% in the monotherapy arm. These rates were slightly higher, however, than that seen with obinutuzumab plus chlorambucil (0.6%). As expected, bleeding events were also higher in the acalabrutinib arms vs the chlorambucil arm, consistent with results observed with other BTK inhibitors. Rates of all-grade hypertension were 7.3% with acalabrutinib plus obinutuzumab, 4.5% with acalabrutinib monotherapy, and 3.6% with obinutuzumab plus chlorambucil.

In summary, the combination of acalabrutinib plus obinutuzumab was superior to chlorambucil plus obinutuzumab. Early follow-up data show excellent disease control and progression-free survival. There was a trend toward improved outcomes with the combination of acalabrutinib plus obinutuzumab vs acalabrutinib alone.

A VHA Real-World Analysis

Much research has focused on the real-world experience of CLL, including how novel therapies are being used, their outcomes, and how patients tolerate them. The CLOVER study (CLL Outcomes of Veterans in the Real World) evaluated treatment patterns and outcomes among a large cohort of patients treated in the VHA system.[8] CLL is among the more common cancers in these patients, and can be associated with Agent Orange, which many veterans were exposed to during the Vietnam and Korean wars.[9] This study examined data for patients treated from 2013 to 2018 with novel therapies for CLL. The study identified 1205 patients, but excluded 161 from the final analysis. Ibrutinib was by far the most common treatment, administered to 922 patients. The other novel treatments were idelalisib, received by 45 patients, and venetoclax, received by 77 patients.

Patients ranged in age from 48 to 96 years. Overall, a quarter of the patients required dose reductions, and almost a third discontinued treatment because of adverse events. Among patients who received ibrutinib, the rate of treatment discontinuation for any reason was 33% among treatment-naive patients and 35% among relapsed/refractory patients. Corresponding rates were 21% and 14% in clinical trials.[7,10-14] Previous analyses of real-world data have shown that discontinuation rates can reach 40% in some cohorts of patients, particularly the elderly.[15] In the CLOVER analysis, rates of discontinuation because of adverse events among patients treated with ibrutinib were 12% in treatment-naive patients and 22% in relapsed/refractory patients. Dose reductions were precipitated by adverse events such as rash, bleeding, infection, and atrial fibrillation. These adverse events are known to be associated with ibrutinib.[11,12] The reasons for discontinuation because of adverse events were similar to those seen in previous studies, and included atrial fibrillation, bleeding, infection, and diarrhea.

Another important observation of this analysis is that discontinuation typically occurs early in the treatment course. The median duration to ibrutinib discontinuation was approximately 8 months in treatment-naive patients and 12 months in relapsed/refractory patients. This finding is not unusual; in earlier clinical trials, most patients who discontinued ibrutinib did so in the first 6 to 12 months.[11-14]

The use of idelalisib has been associated with diarrhea, pneumonitis, transaminitis, and infectious complications.[16] This experience was reflected in the VHA population. An interesting observation is that adverse events more frequently led to treatment discontinuation (84%) rather than dose reduction (16%). Clinicians were more likely to stop idelalisib rather than try to manage complications with dose reductions. The median time to discontinuation of idelalisib was approximately 5 months. Confirming earlier observations, a group of patients stopped treatment early, and then another group stopped after 4 to 6 months. Neutropenia was another frequent cause of discontinuation for idelalisib.

With regards to venetoclax, the median time to treatment discontinuation was approximately 5 months. Many of the discontinuations were because of adverse events, which most frequently consisted of anemia, neutropenia, thrombocytopenia, and resulting infections. Dose reduction was required in 28% of patients, and 31% discontinued treatment. These numbers are concerning for the high-risk population in which venetoclax is typically used in a time-limited manner. It appears, however, that a significant number of the patients cannot tolerate this duration, even when clinicians used dose reductions, growth factors, and other strategies to maximize treatment duration.

The VHA analysis raises several important points. The experience

with ibrutinib and idelalisib in the real-world setting is inferior to that reported in clinical trials and consistent with earlier reports. Additionally, although clinicians are becoming more comfortable using venetoclax, patients are stopping treatment much earlier than might be expected based on previous studies and even other real-world experiences. These outcomes, however, are probably related to the underlying comorbidities in this patient cohort. The prevalence of coronary artery disease ranged from 18% in relapsed/refractory patients treated with ibrutinib or venetoclax to 33% among relapsed/refractory patients treated with idelalisib.

Acalabrutinib, Venetoclax, and Obinutuzumab

A phase 2 study evaluated acalabrutinib, venetoclax, and obinutuzumab as frontline therapy.[17] Acalabrutinib is an exciting alternative BTK inhibitor approved for the treatment of patients with CLL. Early data suggest that acalabrutinib is well tolerated, and possibly better tolerated than ibrutinib.[18]

This single-arm, phase 2 study combined acalabrutinib with venetoclax and obinutuzumab in a sequential manner. Patients began treatment with acalabrutinib in month 1. They then received obinutuzumab in month 2. After 3 months, venetoclax was initiated. Obinutuzumab was administered for 6 months. Treatment with acalabrutinib and venetoclax continued beyond 6 months, for a total of 24 months of therapy. The trial accrued 37 patients, with a median age of 63 years. The study enrolled patients with low-risk or high-risk disease. Any type of *TP53* aberration was seen in 27% of patients. The *TP53* mutation and 17p deletion together were present in 21.6%.

The response rate to the triplet therapy was 100%. At an interim staging at cycle 8, 67.8% of patients had undetectable minimal residual disease (MRD) in the peripheral blood. Nearly half of patients had undetectable MRD in the bone marrow, as assessed by an 8-color flow-based assay with a sensitivity of up to 10^{-4} (1 CLL cell in 10,000 leukocytes). In this study, patients with an undetectable MRD after 24 months of therapy stopped all treatment.

Therapy was fairly well tolerated, with fatigue and headaches being the most frequent adverse events. Bruising was reported in 46% of patients, but most cases were low grade. There were few reports of cardiovascular issues. Thrombocytopenia, neutropenia, and anemia are known side effects of the combination, and they occurred at an expected incidence in this study. Similarly, infusion reactions were infrequent, observed in 19% of patients, with 3% experiencing grade 3 or higher events. With the utilization of debulking therapy for 2 months before the start of venetoclax, tumor lysis was observed in only 2 patients in the study, and both cases occurred prior to initiation of venetoclax. These preliminary results support findings from earlier studies showing that a triplet combination of acalabrutinib, obinutuzumab, and venetoclax is safe and effective. Patients can achieve deep remissions that, in the future, might allow discontinuation of therapy. Moreover, this regimen is also being compared with chemoimmunotherapy in a randomized clinical trial.[19] Multiple trials of similar triplet regimens of alternative agents are ongoing.[19-21]

Measurement of peripheral blood and bone marrow MRD is an established and frequently utilized surrogate survival endpoint that is employed in a multitude of clinical trials of novel therapies. However, there is no standardized approach to the measurement of MRD in the United States, and the availability and use of both flow-based and polymerase chain reaction–based assays are limited. Moreover, there are limited data on long-term outcomes of patients who discontinue treatment based on MRD-negative status. These issues are being actively addressed in ongoing clinical trials.

Zanubrutinib

A phase 1/2 trial examined the selective irreversible BTK inhibitor zanubrutinib in patients with CLL/small lymphocytic leukemia.[22] Zanubrutinib is currently approved for relapsed/refractory mantle cell lymphoma.[23] The CLL cohort included 122 patients, none of whom had received previous treatment with a BTK inhibitor. Eighteen percent of patients had not received any prior treatment. The median number of prior therapies was 2. The median age was 67 years, and the trial included a mix of younger and older patients. Deletion 17p and *TP53* mutations were reported in 10% to 13%, a fairly typical range for the general CLL population. Unmutated immunoglobulin heavy chain variable (*IGHV*) was present in 68% of patients.

The trial reported a response rate of 100% among patients with treatment-naive disease and 95% among those with relapsed/refractory disease. Interestingly, complete response rates were similar in the treatment-naive and relapsed/refractory cohorts (13.6% vs 14.3%). With a median follow-up of 25 months, the rate of progression-free survival was 95% in the treatment-naive cohort and 88% in the relapsed/refractory cohort.

With regard to safety, almost a third of patients had diarrhea, and a quarter had headaches. Infections and cytopenias were also reported. These adverse events have been seen with the other BTK inhibitors. All-grade minor bleeding was reported in approximately 30%. A major hemorrhage occurred in 2% of patients. Bleeding events consisting of contusion, hematuria, petechia, or purpura occurred in 57%. Atrial fibrillation was reported in 3%, and hypertension was seen in 8%. The rate of secondary malignancies was approximately 20%.

Zanubrutinib may be a potential option for the small cohort of patients

who are not candidates for ibrutinib or acalabrutinib. However, additional data and follow-up are required to determine the long-term efficacy in patients with high-risk CLL.[24]

Ibrutinib Combinations

Updated results were presented from the Eastern Cooperative Oncology Group (ECOG) E1912 study, which compared ibrutinib plus rituximab vs fludarabine, cyclophosphamide, and rituximab (FCR) in young patients with previously untreated CLL.[25] Previous data have established clear advantages in overall survival and progression-free survival with the use of ibrutinib plus rituximab as compared with FCR.[26] A remaining issue concerns patients with mutated *IGHV*, in whom ibrutinib plus rituximab does not significantly improve progression-free survival vs FCR. Extended follow-up of these patients in the ECOG E1912 study identified a trend toward improvement in progression-free survival with ibrutinib plus rituximab, but the difference was not statistically significant. This finding will still influence some clinicians to use chemoimmunotherapy in younger patients with mutated *IGHV*.

Similarly, the Alliance A041202 trial of older patients also showed that ibrutinib combinations were better than chemoimmunotherapy.[3] However, there was a higher incidence of sudden death and cardiovascular toxicity among older patients treated with ibrutinib.

Conclusion

Multiple new therapeutic options and combination regimens are now available that are generally well tolerated and extremely effective for the majority of patients with CLL. Moreover, chemoimmunotherapy has an increasingly limited role in the routine management of patients with CLL. The use of MRD assessment as a surrogate for clinical outcomes is also being routinely utilized to guide treatment discontinuation decisions.

Disclosure

Dr Awan has served as a consultant for Gilead, Genentech, Roche, DAVA Oncology, AbbVie, Kite Pharma, Blueprint Medicine, Sunesis, Pharmacyclics, AstraZeneca, Janssen, Celgene, and Karyopharm.

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

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosage

CALQUENCE as Monotherapy

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

CALQUENCE in Combination with Obinutuzumab

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

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

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

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

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

Recommended Dosage for Drug Interactions

Dose Modifications for Use with CYP3A Inhibitors or Inducers

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

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

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

Concomitant Use with Gastric Acid Reducing Agents

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

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

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

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

Table 2: Recommended Dose Modifications for Adverse Reactions

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

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

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

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

Chronic Lymphocytic Leukemia

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

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

ELEVATE-TN

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

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

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

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

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

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

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

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

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

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

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE (CALQUENCE in combination with obinutuzumab and monotherapy) included:
- *Neoplasms:* second primary malignancy (10%), non-melanoma skin cancer (5%)
- *Cardiac disorders:* atrial fibrillation or flutter (3.6%), hypertension (5%)
- *Infection:* herpesvirus infection (6%)

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

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

*Per NCI CTCAE version 4.03
[a] Excludes electrolytes

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

ASCEND

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

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

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

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

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

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

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

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

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE included:
- *Skin and subcutaneous disorders*: bruising (10%), rash (9%)
- *Neoplasms*: second primary malignancy (12%), non-melanoma skin cancer (6%)
- *Musculoskeletal and connective tissue disorders*: arthralgia (8%)
- *Cardiac disorders*: atrial fibrillation or flutter (5%), hypertension (3.2%)
- *Infection*: herpesvirus infection (4.5%)

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

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

Per NCI CTCAE version 5
[a] Excludes electrolytes

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Pregnancy

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

Contraception

Females

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

Pediatric Use

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

Geriatric Use

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

Hepatic Impairment

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

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CALQUENCE®
(acalabrutinib) 100 mg capsules

NOW APPROVED FOR CLL/SLL

Learn more at **CALQUENCEhcp.com**

CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma.

Indication and Usage

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

Select Safety Information

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

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

Reference: CALQUENCE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.

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

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