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A SPECIAL MEETING REVIEW EDITION

Highlights in Chronic Lymphocytic Leukemia From the 2020 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2020 ASCO Meeting

Special Reporting on:

- Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia: ASCEND Final Results
- Initial Results of a Multicenter, Investigator-Initiated Study of MRD-Driven, Time-Limited Therapy With Zanubrutinib, Obinutuzumab, and Venetoclax
- Acalabrutinib in Treatment-Naive Chronic Lymphocytic Leukemia: Mature Results From a Phase 2 Study Demonstrating Durable Remissions and Long-Term Tolerability
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PLUS Meeting Abstract Summaries

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Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia: ASCEND Final Results

Acalabrutinib is a next-generation covalent Bruton tyrosine kinase (BTK) inhibitor associated with less off-target kinase inhibition than the first-generation BTK inhibitor ibrutinib.[1] In clinical studies, acalabrutinib has demonstrated activity in patients with both treatment-naive and relapsed or refractory chronic lymphocytic leukemia (CLL), including those with high-risk features.[2]

Ghia and colleagues discussed the final results of ASCEND, a multicenter, open-label, phase 3 study that compared acalabrutinib monotherapy with standard-of-care combination treatment in patients with relapsed or refractory CLL.[3,4] In the ASCEND trial, a total of 310 patients were randomly assigned in a 1:1 ratio to receive acalabrutinib (100 mg orally twice daily) or the investigator's choice of combination treatment consisting of either oral idelalisib at 150 mg twice daily or intravenous [IV] bendamustine at 70 mg/m^2, both given with rituximab.

In a preplanned interim analysis of the ASCEND trial (performed at a median follow-up of 16.1 months), single-agent acalabrutinib significantly improved the primary endpoint of investigator-assessed progression-free

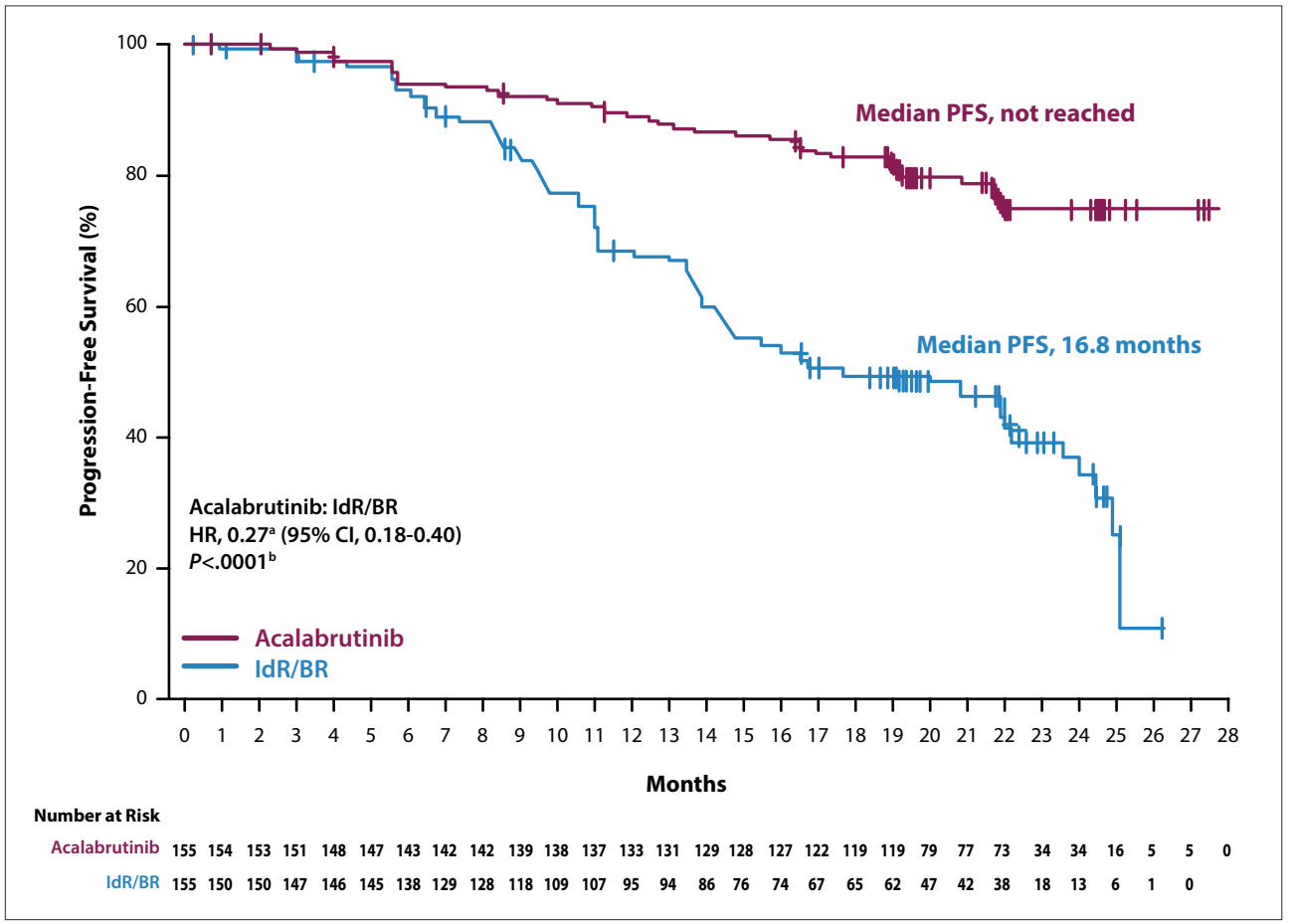

Figure 1. Progression-free survival as assessed by investigators in the phase 3 ASCEND trial, which compared acalabrutinib monotherapy with standard-of-care combination treatment in patients with relapsed or refractory chronic lymphocytic leukemia. The HR was based on a stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in an interactive voice/web response system. The *P* value was based on a log-rank test stratified in the same manner. HR, hazard ratio; IdR/BR, idelalisib plus rituximab/bendamustine plus rituximab; NR, not reached; PFS, progression-free survival. Adapted from Ghia P et al. ASCO abstract 8015. *J Clin Oncol.* 2020;38(15 suppl).[3]

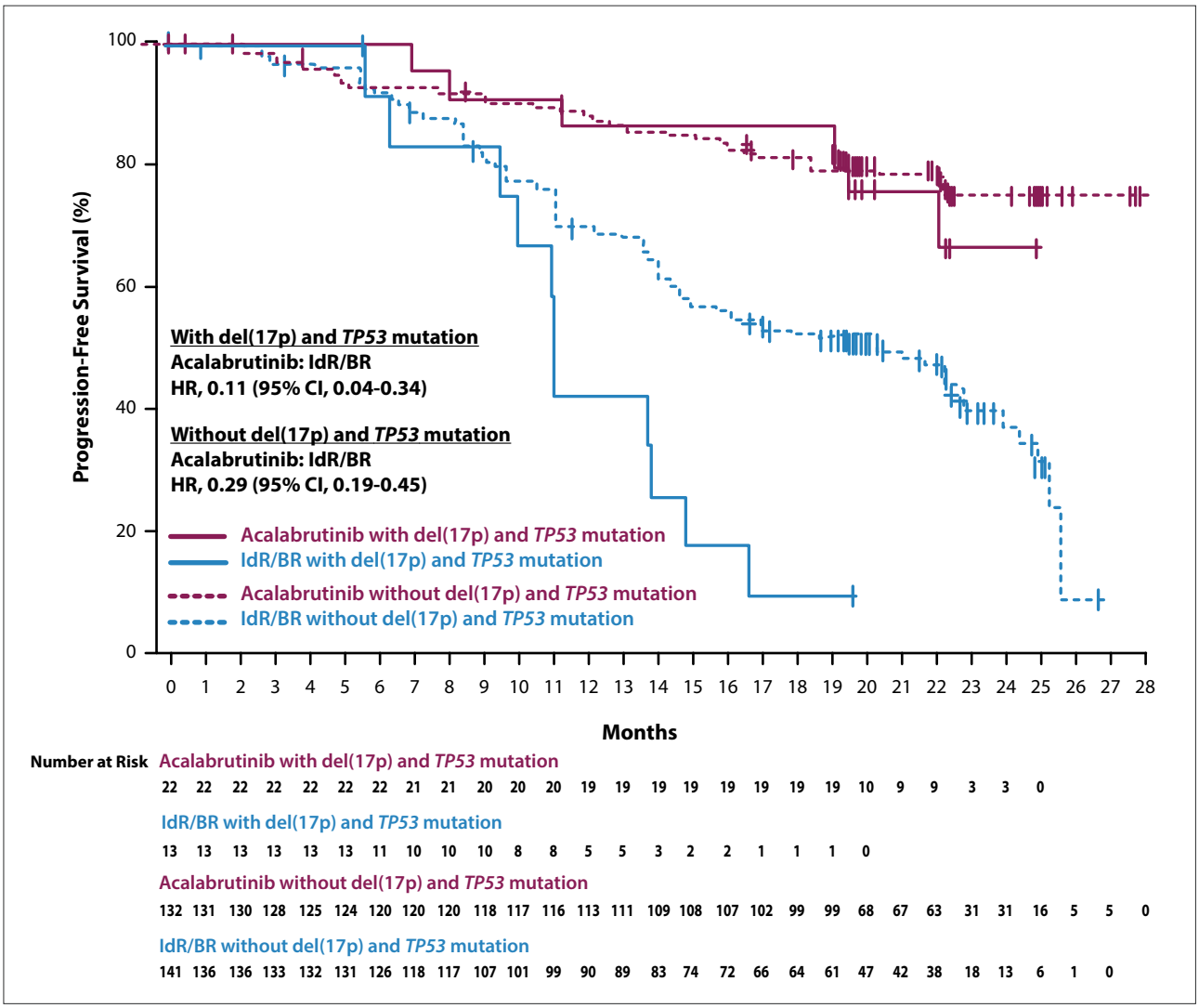

Figure 2. Investigator-assessed progression-free survival in the phase 3 ASCEND trial according to del(17p) and *TP53* mutation status. HR, hazard ratio; IdR/BR, idelalisib plus rituximab/bendamustine plus rituximab. PFS, progression-free survival. Adapted from Ghia P et al. ASCO abstract 8015. *J Clin Oncol.* 2020;38(15 suppl).[3]

survival (PFS) compared with the investigator's choice of therapy. The final results of the ASCEND trial reflected an additional 6 months of follow-up.

After a median follow-up of 22 months, PFS was longer in the acalabrutinib arm than in the investigator's choice of treatment arm. The estimated 18-month PFS rates were 82% (95% CI, 75%-87.3%) vs 48% (95% CI, 39.6-55.8), respectively. The median PFS was not reached with acalabrutinib vs 16.8 months with the investigator's choice of treatment (hazard ratio [HR], 0.27; 95% CI, 0.18-0.40; *P*<.0001; Figure 1). Acalabrutinib also prolonged PFS among patients with high-risk features, including del(17p), a *TP53* mutation (Figure 2), or an unmutated immunoglobulin heavy chain (*IGHV*) gene, as well as in other prespecified subgroups.

The median overall survival (OS), a secondary endpoint, was not reached in either treatment arm. The investigator-assessed overall response rate (ORR) was similar in the 2 groups, at 80% (95% CI, 73%-86%) in the acalabrutinib arm and 84% (95% CI, 77%-89%) in the investigator's choice arm (*P*=.35). However, the median duration of response was longer with acalabrutinib monotherapy than with the investigator's choice of treatment; the median duration of response was not reached in the acalabrutinib arm vs 18.0 months in the investigator's choice arm (HR, 0.19; 95% CI, 0.11-0.33).

The median duration of exposure to treatment with acalabrutinib monotherapy was 21.9 months (range, 1.1-27.9) vs 11.5 months with idelalisib plus rituximab (range, 0.1-27.2) and 5.6 months with bendamustine plus rituximab (range, 1.0-7.1). The rate of treatment discontinuation owing to

adverse events was 56% in the idelalisib/rituximab arm, 16% in the acalabrutinib monotherapy arm, and 17% in the bendamustine/rituximab arm.

The rates of grade 3 or higher treatment-emergent adverse events, serious adverse events, and treatment-related adverse events were higher with idelalisib plus rituximab than with acalabrutinib monotherapy or bendamustine plus rituximab.

In the acalabrutinib arm, the most common adverse events of any grade included headache (22%), neutropenia (21%), diarrhea (20%), and upper respiratory tract infections (20%); most of the events were grade 1 or 2. The most common grade 3 or higher adverse events in the acalabrutinib arm were neutropenia (17%) and anemia (12%). Bleeding events of any grade occurred in 29% of the acalabrutinib arm vs 8% in the investigator's choice arm. The incidence of major hemorrhage was 3% in both treatment arms. Infections of any grade were reported in 63% of the acalabrutinib-treated patients and in 65% of the patients treated with the investigator's choice of therapy. The incidences of all other adverse events of clinical interest, such as atrial fibrillation, hypertension, second primary malignancies (excluding nonmelanoma skin cancer), and tumor lysis syndrome (TLS), were relatively low and similar in the 2 treatment arms.

ABSTRACT SUMMARY Cause of Death in Patients With Newly Diagnosed Chronic Lymphocytic Leukemia Stratified by the CLL-International Prognostic Index

A study correlated the causes of death in 1276 patients who died after a new diagnosis of CLL with level of risk according to the International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI) (Abstract 8026). Risk was categorized as low in 35%, intermediate in 35%, and high or very high in 30%. Among patients with high-risk or very high-risk CLL, the cumulative incidence of death from CLL progression was 17.3% at 5 years and 30.3% at 10 years. These rates were significantly higher ($P<.001$) than those for patients with intermediate-risk CLL (2.0% and 10.4%, respectively) or low-risk CLL (0.3% and 2.8%, respectively). Among patients with high-risk or very high-risk disease, the incidence of deaths from infection or a second malignancy was 5.7% at 5 years and 12.9% at 10 years. In patients with low-risk CLL, the cumulative incidence of death from these causes was 2.1% at 5 years and 6.4% at 10 years.

References

1. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): a covalent Bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. *J Pharmacol Exp Ther.* 2017;363(2):240-252.
2. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2016;374(4):323-332.
3. Ghia P, Pluta A, Wach M, et al. Acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed/refractory chronic lymphocytic leukemia: ASCEND final results [ASCO abstract 8015]. *J Clin Oncol.* 2020;38(15 suppl).
4. Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia [published online May 27, 2020]. *J Clin Oncol.* doi:10.1200/JCO.19.03355.

Initial Results of a Multicenter, Investigator-Initiated Study of MRD-Driven, Time-Limited Therapy With Zanubrutinib, Obinutuzumab, and Venetoclax

The combination of venetoclax and obinutuzumab is an FDA-approved regimen for the initial treatment of CLL; approval was based on results from the CLL14 trial.[1] This time-limited regimen (administered over a period of 1 year) is associated with high rates of undetectable minimal residual disease (uMRD); peripheral blood uMRD has been reported in 76% of patients. Preclinical data have shown synergistic activity between venetoclax and a BTK inhibitor, a finding that was supported in early-phase trials.[2,3] Importantly, these combinations appear relatively safe, although neutropenia occurred in 35% to 51% of patients in these studies.

Zanubrutinib is a potent, specific, irreversible second-generation BTK inhibitor that is approved for the treatment of patients with relapsed/refractory mantle cell lymphoma (MCL).[4] In the phase 3 ASPEN trial of zanubrutinib vs ibrutinib for the treatment of Waldenström macroglobulinemia, zanubrutinib was associated with a lower incidence of atrial fibrillation, severe bleeding, diarrhea, and rash compared with ibrutinib.[5] Zanubrutinib also minimally inhibits interleukin 2–inducible T-cell kinase, a protein that is critical for engaging antibody-dependent cell-mediated cytotoxicity (ADCC).[6,7] Thus, zanubrutinib may be preferred in combination with a CD20-directed monoclonal antibody such as obinutuzumab, whose mechanism of action includes ADCC. Additionally, on-treatment lymph node biopsies in the phase 1 dose-escalation study of zanubrutinib confirmed 100% occupancy of BTK within the lymph nodes of treated patients.[8]

Based on these data, researchers hypothesized that zanubrutinib could be combined with venetoclax and obinutuzumab to achieve more fre-

quent uMRD responses. Additionally, it was hypothesized that a uMRD-driven treatment duration strategy could be used to facilitate successful treatment discontinuation and durable post-treatment responses. Soumerai and colleagues presented initial results from a multicenter, investigator-initiated, phase 2 study of MRD-driven, time-limited therapy with zanubrutinib, obinutuzumab, and venetoclax (BOVen) among patients with previously untreated CLL or small lymphocytic lymphoma (SLL) with leukemic involvement.[9]

In the BOVen regimen, patients received a 2-month lead-in treatment, with the goal of reducing risk for TLS.[9] Zanubrutinib was administered at a dose of 160 mg twice daily, with obinutuzumab given at a dose of 1000 mg on days 1, 8, and 15 during cycle 1; then on day 1 only of cycles 2 through 8. TLS risk was reassessed before cycle 3, after which venetoclax was initiated with the recommended 5-week ramp-up to the target dose (400 mg daily). Patients then completed 6 cycles of the BOVen triplet combination. Thereafter, treatment was determined by a prespecified uMRD endpoint. Peripheral blood was assessed for uMRD every 2 months beginning with cycle 7. The minimum duration of therapy was 6 months, and the maximum duration was 24 months. A peripheral blood uMRD response triggered an evaluation for bone marrow MRD. A bone marrow uMRD response triggered computed tomography–based imaging to assess response (according to criteria from the International Workshop on Chronic Lymphocytic Leukemia [iwCLL]). Following confirmation of uMRD in the bone marrow, patients completed an additional 2 cycles of therapy. They could then discontinue treatment and enter post-treatment surveillance after confirmation of ongoing uMRD in the peripheral blood.

The primary endpoint of the study is the rate of confirmed uMRD responses in the blood and bone marrow of treated patients, determined by flow cytometry at a sensitivity of 10^{-4}. Selected secondary endpoints include the time on therapy required to achieve a uMRD response, the proportion of patients who successfully discontinued therapy, the effect of lead-in therapy with zanubrutinib plus obinutuzumab on TLS risk assignment, and safety and tolerability.[9]

Key eligibility criteria for patient enrollment included a diagnosis of CLL or SLL with leukemic-phase disease that required treatment per iwCLL criteria. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate hematologic function. The study enrolled patients receiving treatment with antiplatelet and anticoagulation therapy, but not dual antiplatelet therapy.[9]

From March to October 2019, 39 patients were enrolled. Their median age was 59 years (range, 23-73), with a 3-to-1 male predominance. A total of 72% of the patients had high-risk or very high-risk features. For example, 72% had an unmutated *IGHV* gene, and 15% had a *TP53* aberration. Mutations were also noted in the *ATM*, *NOTCH1*, and *SF3B1* genes, among others.[9]

The most common treatment-emergent adverse events of all grades were neutropenia (in 51.3%), thrombocytopenia (in 46.2%), infusion-related reactions (in 41%), bruising (in 41%), and diarrhea (in 41%). The few adverse events of grade 3 or higher consisted primarily of neutropenia and thrombocytopenia. Grade 3/4 neutropenia (an adverse event of special interest) occurred in 15.4% of

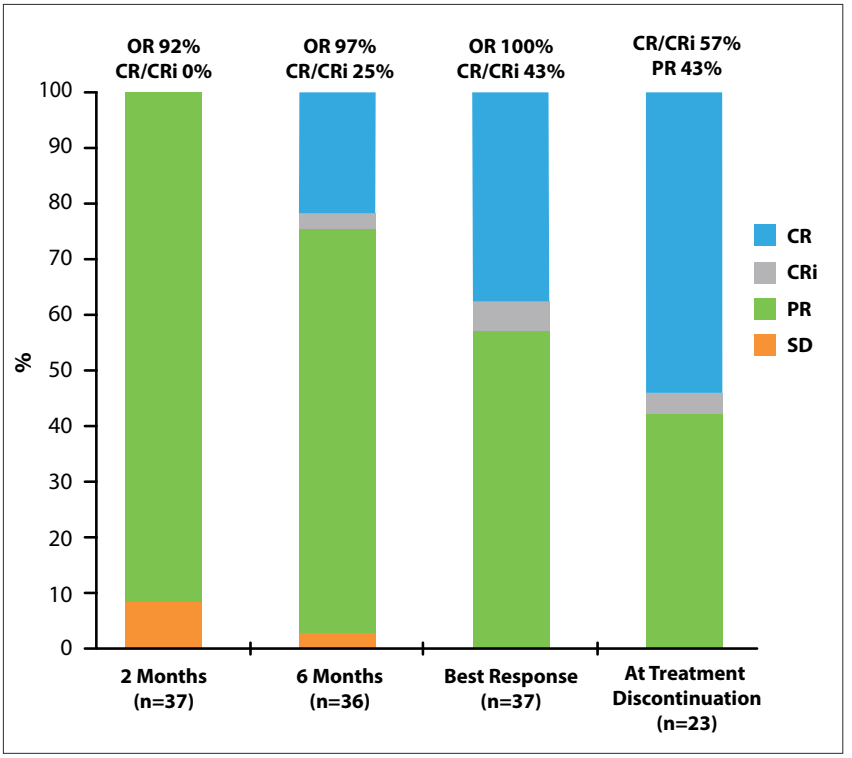

Figure 3. Overall response rates according to iwCLL criteria in a phase 2 study evaluating time-limited therapy with zanubrutinib, obinutuzumab, and venetoclax in patients with previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma with leukemic involvement. CR, complete response; CRi, complete response with incomplete marrow recovery; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; OR, overall response; PR, partial response; SD, stable disease. Adapted from Soumerai JD et al. ASCO abstract 8006. *J Clin Oncol.* 2020;38(15 suppl).[9]

ABSTRACT SUMMARY Impact of Premature Venetoclax Discontinuation/Interruption on Outcomes in Relapsed/Refractory Chronic Lymphocytic Leukemia: Phase III MURANO Study Results

The phase 3 MURANO study compared venetoclax plus rituximab vs bendamustine plus rituximab in patients with relapsed/refractory CLL. An analysis of 194 patients treated with venetoclax/rituximab found that 28% of these patients prematurely discontinued venetoclax. Among those who discontinued, 54% did so because of an adverse event and 22% because of disease progression (Abstract 8028). Premature discontinuation of venetoclax (for reasons other than disease progression) resulted in a shorter median PFS of 24.3 months. The median PFS was 52.3 months among all patients treated with venetoclax/rituximab and not reached among patients who completed venetoclax treatment. However, other forms of dose modification (eg, dose interruption or dose reduction, which occurred in 71% of patients) had no effect on either PFS or OS.

patients, with 1 case of febrile neutropenia. Grade 3 thrombocytopenia was reported in 5.1% of patients; no grade 4 events occurred. A grade 4 infusion-related reaction occurred in 1 patient (2.6%), and 1 patient had a grade 5 intracranial hemorrhage on day 1 of cycle 1. This patient had started protocol therapy as an inpatient, and IV heparin had been initiated for new pulmonary emboli within 2 days after the start of protocol therapy. Recurrent atrial fibrillation developed during the study in 1 patient with a history of paroxysmal atrial fibrillation and other cardiac comorbidities.

At study entry, 43% of patients were at high risk for TLS; this rate dropped to 5% following lead-in treatment with zanubrutinib plus obinutuzumab. No patients developed laboratory or clinical TLS during venetoclax ramp-up treatment.

After a median follow-up of 11 months (range, 2-14+), the rate of uMRD was 83.8% in the peripheral blood and 73% in the bone marrow.[9] The median time to bone marrow uMRD was 6 months (range, 2-14+). The prespecified endpoint of uMRD was achieved in 62% of patients, all of whom discontinued therapy after a median of 8 months. The ORR was 100%, with a complete response (CR) or a complete response with incomplete marrow recovery (CRi) reported in 43% (Figure 3).

References

1. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380(23):2225-2236.
2. Tam CS, Siddiqi T, Allan JN, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): results from the MRD cohort of the phase II CAPTIVATE study [ASH abstract 35]. *Blood*. 2019;134(suppl 1).
3. Jain N, Keating M, Thompson P, et al. Ibrutinib and venetoclax for first-line treatment of CLL. *N Engl J Med*. 2019;380(22):2095-2103.
4. Guo Y, Liu Y, Hu N, et al. Discovery of zanubrutinib (BGB-3111), a novel, potent, and selective covalent inhibitor of Bruton's tyrosine kinase. *J Med Chem*. 2019;62(17):7923-7940.
5. Tam CSL, Opat S, D'Sa S, et al. ASPEN: results of a phase III randomized trial of zanubrutinib versus ibrutinib for patients with Waldenström macroglobulinemia (WM) [ASCO abstract 8007]. *J Clin Oncol*. 2020;38(15 suppl).
6. Flinsenberg TWH, Tromedjo CC, Hu N, et al. Differential effects of BTK inhibitors ibrutinib and zanubrutinib on NK-cell effector function in patients with mantle cell lymphoma. *Haematologica*. 2020;105(2):e76-e79.
7. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet*. 2020;395(10232):1278-1291.
8. Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood*. 2019;134(11):851-859.
9. Soumerai JD, Mato AR, Carter J, et al. Initial results of a multicenter, investigator initiated study of MRD driven time limited therapy with zanubrutinib, obinutuzumab, and venetoclax [ASCO abstract 8006]. *J Clin Oncol*. 2020;38(15 suppl).

Acalabrutinib in Treatment-Naive Chronic Lymphocytic Leukemia: Mature Results From a Phase 2 Study Demonstrating Durable Remissions and Long-Term Tolerability

Targeted inhibition of BTK has improved clinical outcomes among patients with relapsed/refractory or treatment-naive CLL. Acalabrutinib is a selective BTK inhibitor that has demonstrated less off-target activity in vitro than other BTK inhibitors, such as ibrutinib.[1] In late 2019, acalabrutinib was approved for the treatment of patients with CLL on the basis of favorable results from 2 distinct phase 3 studies (ELEVATE-TN and ASCEND).[2,3]

Byrd and colleagues presented mature results of ACE-CL-001, the first phase 2 study of acalabrutinib in patients with treatment-naive CLL.[4] The expansion phase of this study enrolled 99 patients with treatment-naive disease. The patients received acalabrutinib until disease progression or unacceptable toxicity. Patients initially received a dose of either 100 mg twice daily or 200 mg once daily. Later in the study, however, with evidence showing that twice-daily dosing was potentially more beneficial, all patients received 100 mg twice daily. In addition to an assessment of tolerability, the efficacy endpoints of ACE-CL-001

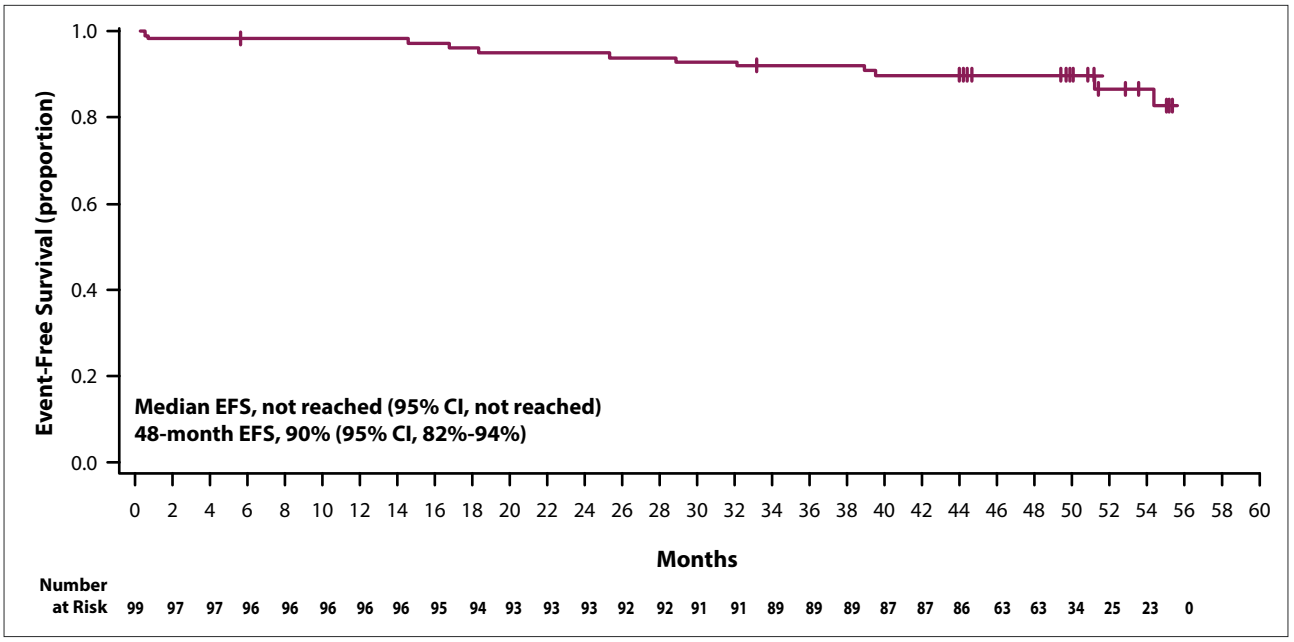

Figure 4. Event-free survival in the phase 2 ACE-CL-001 trial, which evaluated acalabrutinib in patients with treatment-naive chronic lymphocytic leukemia. Adapted from Byrd JC et al. ASCO abstract 8024. *J Clin Oncol.* 2020;38(15 suppl).[4]

included investigator-assessed ORR, time to response, duration of response, and event-free survival (EFS).[4]

The median age of enrolled patients was 64 years (range, 33-85), and 46% of the patients were ages 65 years or older. The median time from initial diagnosis of CLL to the first dose of treatment was 3.4 years (range, 0.1-16.5). Nearly half (47%) of patients had Rai stage III or IV disease. High-risk features were well represented, with del(17p) in 10% of patients, unmutated *IGHV* in 62%, mutated *TP53* in 14%, and complex karyotype in 18%.[4]

After a median follow-up of 53 months (range, 1-59), 86% of patients remained on acalabrutinib therapy.[4] A total of 14 patients discontinued acalabrutinib, 6 of them because of adverse events (namely, secondary cancers [n=4] and infections [n=2]). The most common adverse events of any grade were diarrhea (52%), headache (45%), upper respiratory tract infection (44%), arthralgia (42%), and contusion (42%). Most of these adverse events were grade 1 or 2, and they generally resolved with time.

Serious adverse events occurred in 38% of patients; pneumonia (n=4) and sepsis (n=3) were the only ones reported in 2 or more patients. Two deaths were reported during the study, one from multiple-organ dysfunction in the setting of pneumonia and the other from cardiac failure. Both deaths were considered unrelated to acalabrutinib therapy.[4]

ORR as assessed by the investigator was 97%, which included CRs in 7% and partial responses (PRs) in 90%.[4] A response was seen in all patients with a high-risk feature, including 57 patients with unmutated *IGHV*, 12 with complex karyotype, 9 with del(17p), and 9 with mutated *TP53*. The median time to response was 3.7 months (range, 2-22). The median duration of response with extended follow-up was not reached; the estimated 48-month durable response rate was 97% (95% CI, 90%-99%). The median EFS also was not reached; the estimated 48-month EFS rate was 90% (95% CI, 82%-94%; Figure 4).

The study authors concluded that acalabrutinib monotherapy produced a high response rate and a durable response, even in patients with high-risk genomic characteristics.[4] These results support findings from earlier phase 3 studies.[3] The adverse events associated with acalabrutinib were generally mild. Only a small subset of patients discontinued therapy because of adverse events. Reports of hypertension remained uncommon, even with the extended follow-up. No long-term safety signals emerged.

References

1. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): a covalent Bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. *J Pharmacol Exp Ther.* 2017;363(2):240-252.
2. Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia [published online May 27, 2020]. *J Clin Oncol.* 2020;JCO1903355.
3. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet.* 2020;395(10232):1278-1291.
4. Byrd JC, Woyach JA, Furman RR, et al. Acalabrutinib in treatment-naïve chronic lymphocytic leukemia: mature results from phase II study demonstrating durable remissions and long-term tolerability [ASCO abstract 8024]. *J Clin Oncol.* 2020;38(15 suppl).

Long-Term Follow-Up of Anti-CD19 CAR T-Cell Therapy for B-Cell Lymphoma and Chronic Lymphocytic Leukemia

In clinical studies, chimeric antigen receptor (CAR) T-cell therapy was associated with complete remissions in patients with relapsed B-cell lymphoma.[1] The complete remission rate with the approved anti-CD19 CAR T-cell products is 40% to 54%.[2] However, the long-term durability of these responses is unclear.

Cappell and colleagues conducted the first study of anti-CD19 CAR T-cell therapy to show success in the treatment of B-cell lymphoma.[3] This trial evaluated the CAR therapy FMC63-28z, later commercially developed as axicabtagene ciloleucel. Here, the study investigators examined outcomes and long-term adverse events in the first 43 patients with lymphoma treated with anti-CD19 CAR T cells. Three of these patients received a second CAR T-cell infusion, for a total of 46 infusions.

At the time the study was conducted, the optimal lymphodepleting chemotherapy regimen was not clear. Patients were therefore divided into 3 cohorts with various regimens. Patients in cohorts 1 and 2 received the same doses of cyclophosphamide and fludarabine; cohort 1 also received interleukin 2 following cell infusion. Patients in cohort 3 received a lower dose of cyclophosphamide. Cohorts 1 and 2 included a higher number of patients with low-grade lymphomas or CLL. Cohort 3 had more patients with diffuse large B-cell lymphoma (DLBCL) or primary mediastinal large B-cell lymphoma (PMBCL).

At baseline, 65% (n=28) of the patients had DLBCL or PMBCL, 19% (n=8) had low-grade lymphoma, and 16% (n=7) had CLL.[3] In 49% of patients, the disease was refractory to chemotherapy. For 19% of patients, autologous stem cell transplant (ASCT) had been the most recent treatment before study enrollment. Among the patients with CLL, the median CAR T-cell dose was 4×10^6/kg.

In 58% of the patients, the best response was a CR. A PR was the best response in 23% of patients. Among the patients who did not achieve a CR, none had a durable response. In contrast, among the 25 patients who did achieve a CR, 60% of these responses were evaluable and ongoing at the last follow-up visit. The duration of response for ongoing CRs ranged from 43 months to 113 months.

Among the 45 evaluable patients, the median EFS was 55 months, and the median OS was not reached. No differences in EFS or OS were reported on the basis of lymphoma type or assigned cohort (Figure 5). The median EFS for patients who achieved a CR was not reached.[3]

The investigators also correlated levels of CAR T cells with response outcome. The peak CAR T-cell levels of the patients who achieved a CR were higher than those of the patients who did not (*P*=.0041). Similarly, the patients whose duration of response was longer than 3 years had higher peak CAR T-cell levels (*P*=.0051). CAR T-cell levels peaked between days 6 and 17 in all but 4 patients. In these 4 patients, levels peaked between days 26 and 55. The investigators also examined the association between CAR T-cell persistence and response outcome. However, CAR T-cell persistence from days 28 to 56 did not correlate with response or duration of response.[3]

Few adverse events were reported. In the 24 evaluable patients with a CR, 9 (38%) did not recover a normal level of B cells. In 18 of these patients (75%), a low level of at least 1 immunoglobulin persisted for an extended period. After treatment, 7

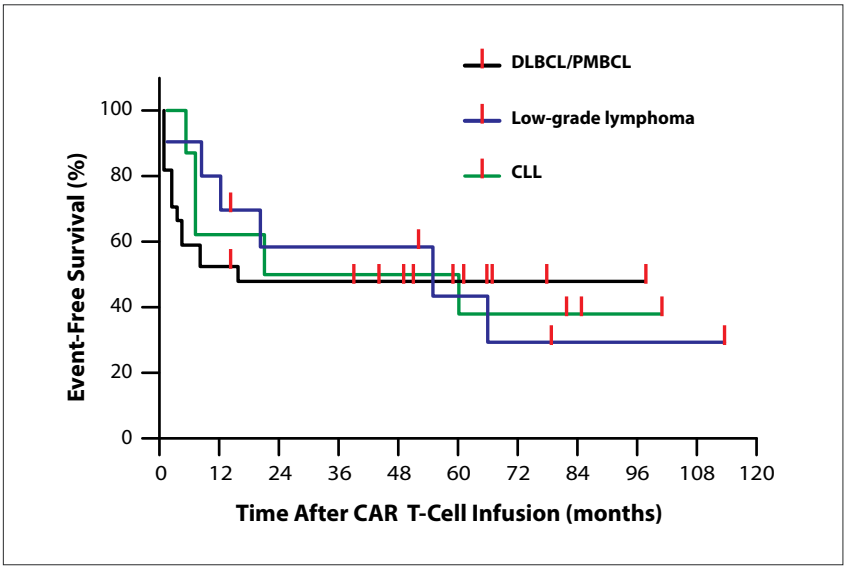

Figure 5. Event-free survival according to disease type in patients with lymphoma treated with anti-CD19 CAR T cells. CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma. Adapted from Cappell KM et al. ASCO abstract 3012. *J Clin Oncol.* 2020;38(15 suppl).[3]

patients developed a second malignancy (a solid tumor malignancy in 5 and myelodysplastic syndrome in 2). The only autoimmune-related adverse event was hypothyroidism, which occurred in 1 patient. Among the entire population of 43 patients, 4 were hospitalized with infections that developed many months (>6) after the CAR T-cell infusion.

B-cell levels recovered to normal in 15 of the 24 evaluable patients who achieved a CR. This CR was ongoing in 10 patients (67%) at the time of the report (median time since B-cell recovery, 50 months).

References

1. Abramson JS. Anti-CD19 CAR T-cell therapy for B-cell non-Hodgkin lymphoma. *Transfus Med Rev.* 2020;34(1):29-33.
2. Chavez JC, Bachmeier C, Kharfan-Dabaja MA. CAR T-cell therapy for B-cell lymphomas: clinical trial results of available products. *Ther Adv Hematol.* 2019;10:2040620719841581.
3. Cappell KM, Sherry RM, Yang JC, et al. Long-term follow-up of anti-CD19 CAR T-cell therapy for B-cell lymphoma and chronic lymphocytic leukemia [ASCO abstract 3012]. *J Clin Oncol.* 2020;38(15 suppl).

Safety of Acalabrutinib Monotherapy in Hematologic Malignancies: Pooled Analysis From Clinical Trials

In vitro, the BTK selectivity of acalabrutinib is superior to that of ibrutinib.[1,2] Fewer off-target effects may improve the safety profile of acalabrutinib.[2-5] A favorable safety profile is supported by the low rates of discontinuation owing to adverse events in clinical trials of this agent across B-cell malignancies.[6-8] Furman and colleagues presented the results of a pooled analysis that aimed to provide an overall summary of the safety profile of acalabrutinib monotherapy across multiple hematologic malignancies.[9]

The analysis included data on safety outcomes from nine phase 1, 2, and 3 studies conducted in patients with CLL/SLL, Richter transformation, Waldenström macroglobulinemia, activated B-cell–like DLBCL, multiple myeloma, follicular lymphoma, MCL, and prolymphocytic leukemia. All patients had received at least 1 dose of acalabrutinib monotherapy.

Among the 1040 patients who were included in the analysis, 35% were treatment-naive, and 65% had relapsed or refractory disease.[9] The median time of follow-up was 26.4 months (range, 0.0-58.5). At the data cutoff, 65% of patients remained on acalabrutinib therapy. A total of 83% of patients

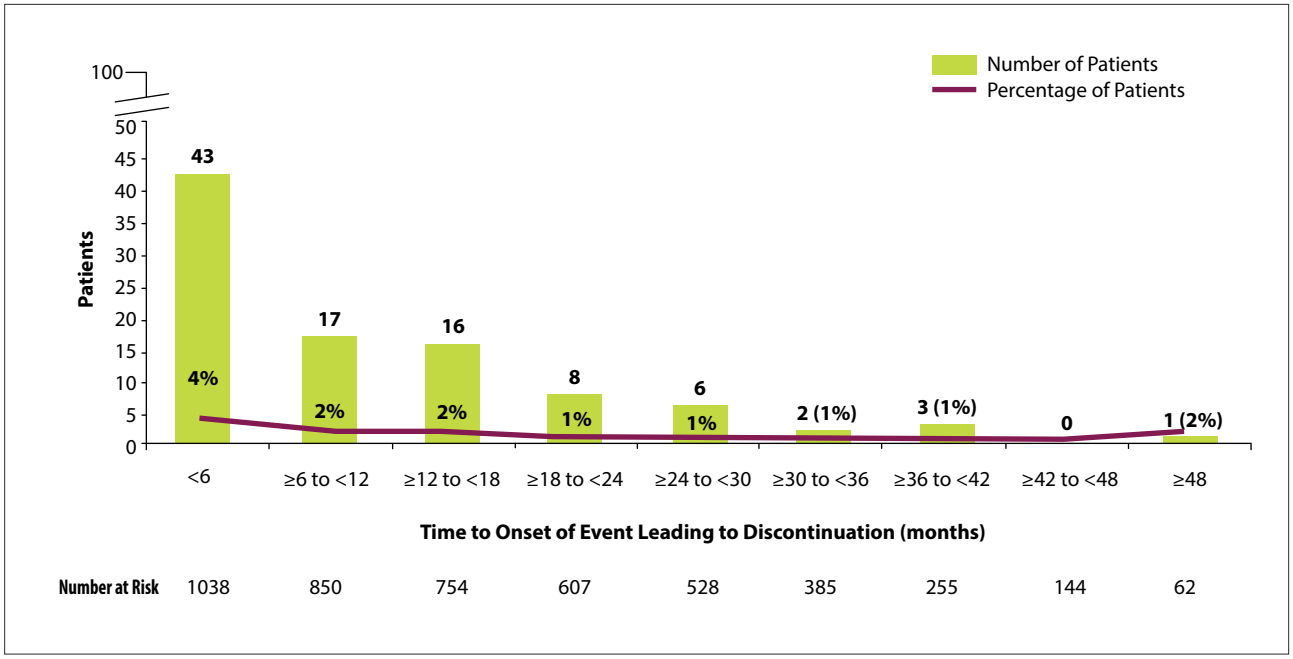

Figure 6. The time to onset of an adverse event that led to treatment discontinuation in a pooled safety analysis of patients treated with acalabrutinib. A patient could be counted once in each time interval if he or she reported multiple events. The percentage during each time period was calculated using the number of patients who were still receiving treatment (at risk) during that time period as the denominator. Adapted from Furman RR et al. ASCO abstract 8064. *J Clin Oncol.* 2020;38(15 suppl).[9]

received a dose of 100 mg twice daily. The median duration of exposure to acalabrutinib was 24.6 months (range, 0.0-58.5), and the median relative dose intensity was 98.7%.

At the data cutoff, 96% of patients had experienced at least 1 adverse event of any grade. The most frequently reported all-grade adverse events included headache (37.8%), diarrhea (36.7%), upper respiratory tract infection (22.0%), contusion (21.7%), nausea (21.7%), fatigue (21.3%), and cough (21.0%). Most of these events were mild (grade 1) or moderate (grade 2). The most common events—headache and diarrhea—occurred during the first 6 months of treatment in 35% and 26% of patients, respectively. The median duration of headache was 20 days (range, 1-994); most headaches resolved and did not recur. One patient discontinued treatment because of headache.

Grade 3 or higher adverse events were reported in 54.1% of patients. The most common of these events were neutropenia (11.2%), anemia (7.8%), and pneumonia (5.1%). Serious adverse events were reported in 39% of patients. Pneumonia, which occurred in 5% of patients, was the most common serious adverse event.

Among the 13% of patients who died, the most frequent causes were disease progression (6%) and adverse events (5%). The most frequent fatal adverse event was pneumonia, occurring in 8 patients (1%). All other fatal events occurred in no more than 3 patients.[9]

Adverse events led to dose modifications in 4% of patients, dose delays in 38%, and treatment discontinuation in 9%. Among the patients who discontinued treatment, most did so because of adverse events that occurred within the first 6 months of therapy (Figure 6).[9]

Infections, an adverse event of clinical interest, occurred in 66.7% of patients. Grade 3 or higher infections occurred in 17.6%. The most common infections were upper respiratory tract infections (22%) and sinusitis (11%). The median time to infection was 97 days (range, 1-1343).

Other adverse events of clinical interest included hemorrhage of any grade (46.3%; Figure 7), atrial fibrillation (4.4%), and hypertension (7.6%). In most patients who experienced hemorrhage of any grade, the event occurred within the first 6 months of treatment. Grade 3 or higher hemorrhage events occurred in 2.7% of patients. Among 40 major hemorrhage events (which occurred in 37 patients), 22 were considered serious. Atrial fibrillation/atrial flutter occurred in 4.4% of patients while on study; 1.3% of these cases were grade 3. No grade 4 or 5 events were reported. The incidence of atrial fibrillation rose at a constant rate of approximately 1% per year and remained low throughout the duration of treatment, with a median time to onset of 522 days.[9]

The investigators concluded that the results of this analysis support the long-term safety of acalabrutinib in patients with multiple types of B-cell malignancies.

References

1. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): a covalent Bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. *J Pharmacol Exp Ther.* 2017;363(2):240-252.
2. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2016;374(4):323-332.
3. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. *Mol Cancer.* 2018;17(1):57.
4. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2013;369(1):32-42.
5. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* 2014;371(3):213-223.
6. Byrd JC, Wierda WG, Schuh A, et al. Acalabrutinib monotherapy in patients with relapsed/refractory chronic lymphocytic leukemia: updated phase 2 results. *Blood.* 2020;135(15):1204-1213.
7. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *Lancet.* 2018;391(10121):659-667.
8. Owen RG, McCarthy H, Rule S, et al. Acalabrutinib monotherapy in patients with Waldenström macroglobulinemia: a single-arm, multicentre, phase 2 study. *Lancet Haematol.* 2020;7(2):e112-e121.
9. Furman RR, Byrd JC, Owen RG, et al. Safety of acalabrutinib monotherapy in hematologic malignancies: pooled analysis from clinical trials [ASCO abstract 8064]. *J Clin Oncol.* 2020;38(15 suppl).

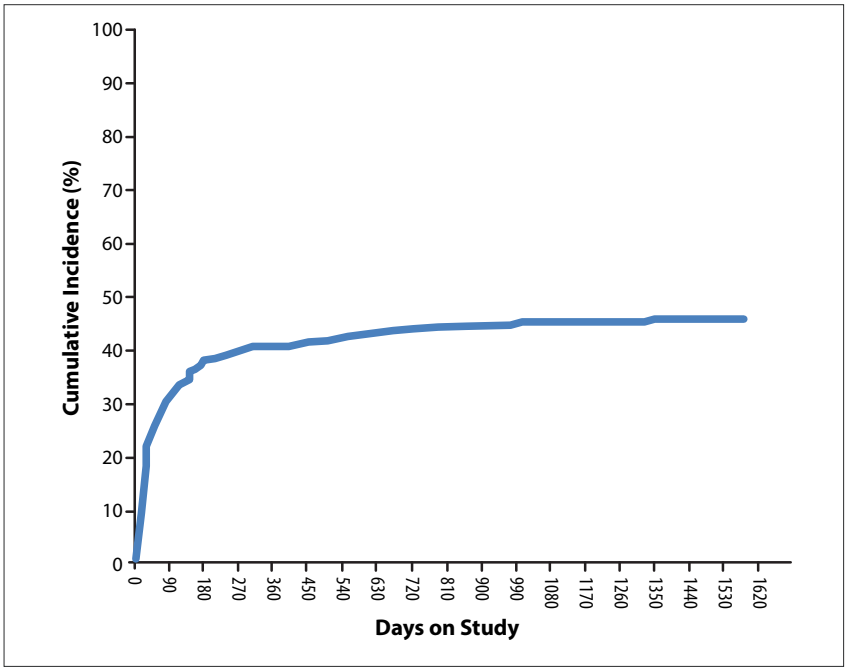

Figure 7. Cumulative incidence of any-grade hemorrhage in a pooled safety analysis of patients treated with acalabrutinib. Adapted from Furman RR et al. ASCO abstract 8064. *J Clin Oncol.* 2020;38(15 suppl).[9]

Fixed-Duration Venetoclax-Obinutuzumab for Previously Untreated Patients With Chronic Lymphocytic Leukemia: Follow-Up of Efficacy and Safety Results From the Multicenter, Open-Label, Randomized, Phase III CLL14 Trial

Al-Sawaf and colleagues summarized the results from CLL14, a randomized phase 3 trial in patients with previously untreated CLL who had coexisting conditions.[1] In CLL14, patients were randomly assigned to receive 6 cycles of obinutuzumab together with either 12 cycles of venetoclax or 12 cycles of chlorambucil. In an earlier analysis of this study, the estimated rate of 24-month PFS was 88.2% with fixed-duration venetoclax/obinutuzumab vs 64.1% with chlorambucil/obinutuzumab.[2]

A total of 432 patients were randomly assigned in a 1:1 ratio to the 2 arms.[1] The primary endpoint of the study was investigator-assessed PFS. After a median observation duration of 39.6 months, the 3-year PFS rate was 81.9% with venetoclax/obinutuzumab vs 49.5% with chlorambucil/obinutuzumab. The median PFS was not reached with venetoclax/obinutuzumab vs 35.6 months with chlorambucil/obinutuzumab (HR, 0.31; 95% CI, 0.22-0.44; *P*<.001; Figure 8).[1]

These PFS benefits were observed across all patient risk groups. Among patients with *TP53* aberrations (deletion and/or mutation), the treatment benefit was greater with venetoclax plus obinutuzumab than with chlorambucil plus obinutuzumab. However, the poor prognosis associated with *TP53* aberrations was not overcome by either combination treatment.[1]

Treatment with venetoclax plus obinutuzumab also benefited patients with unmutated or mutated *IGHV* status. This finding is particularly notable because an earlier follow-up analysis of this study identified no difference in PFS between the 2 treatment arms in patients with mutated *IGHV*. The longer follow-up in this current analysis identified greater efficacy with the venetoclax/obinutuzumab combination among the patients with mutated *IGHV*.[1]

Median OS was not reached in either arm. No difference in OS was observed (HR, 1.03; 95% CI, 0.60-1.75; *P*=.92).

uMRD was reported in 47.2% of the patients treated with venetoclax plus obinutuzumab vs 7.4% in those treated with chlorambucil plus obinutuzumab.[1] A landmark PFS analysis (performed after the end of treatment) included data from different groups of patients according to MRD status. PFS was consistently longest in patients with uMRD or the lowest levels of MRD. Among patients with uMRD, PFS was similar regardless of whether they achieved a CR or a PR.

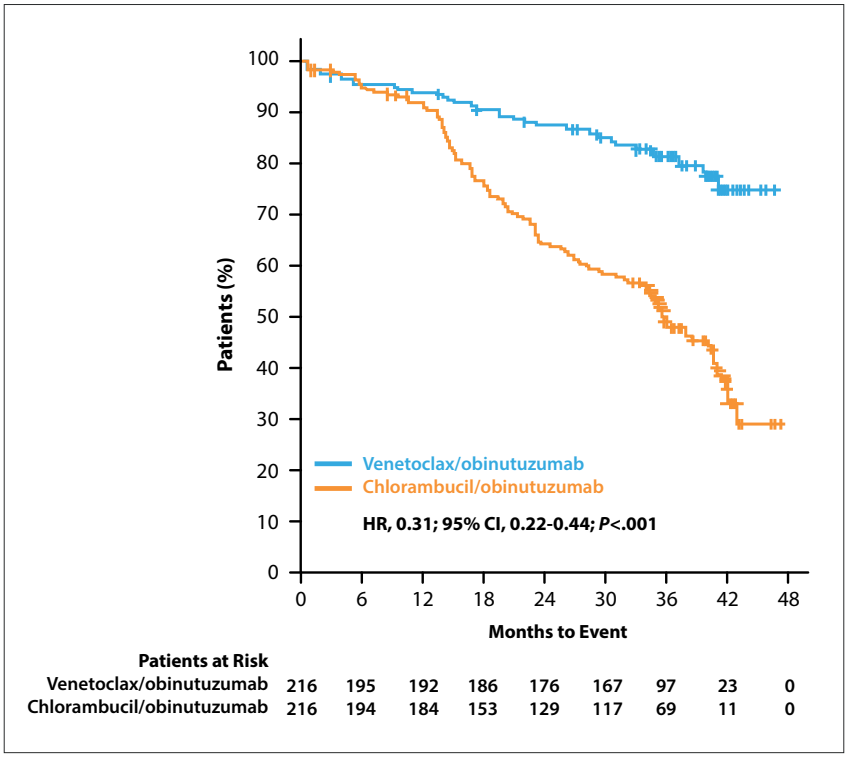

Figure 8. The median progression-free survival in CLL14, a randomized phase 3 trial that compared fixed-duration venetoclax/obinutuzumab vs chlorambucil/obinutuzumab in patients with previously untreated CLL and comorbidities. Adapted from Al-Sawaf O et al. ASCO abstract 8027. *J Clin Oncol.* 2020;38(15 suppl).[1]

References

1. Al-Sawaf O, Zhang C, Tandon M, et al. Fixed-duration venetoclax-obinutuzumab for previously untreated patients with chronic lymphocytic leukemia: follow-up of efficacy and safety results from the multicenter, open-label, randomized, phase III CLL14 trial [ASCO abstract 8027]. *J Clin Oncol.* 2020;38(15 suppl).
2. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med.* 2019;380(23):2225-2236.

Effect of Adding Ublituximab to Ibrutinib on PFS, ORR, and MRD Negativity in Previously Treated High-Risk Chronic Lymphocytic Leukemia: Final Results of the GENUINE Phase III Study

Ublituximab is an investigational anti-CD20 monoclonal antibody that targets a unique epitope on CD20 and induces complement-dependent cytotoxicity (CDC).[1] In addition, ublituximab is glycoengineered to enhance affinity for all variants of the FcgRIIIa receptor. The combination of ublituximab plus ibrutinib showed a high level of clinical activity in a phase 2 study of relapsed/refractory CLL.[2] This result led to the GENUINE study, an open-label, multicenter, randomized phase 3 study comparing the combination of ublituximab plus ibrutinib vs ibrutinib alone in patients with relapsed/refractory high-risk CLL. The trial enrolled patients with del(17p), del(11q), or a *TP53* mutation. Initial data from the GENUINE study indicated improved ORR and uMRD with ublituximab/ibrutinib.[3] At the prior data cutoff, the PFS appeared better with ublituximab/ibrutinib, although the data were still immature.

Sharman and colleagues presented a final analysis of this study, with a median follow-up of 41.9 months.[4] The primary endpoint, ORR as evaluated by independent review committee (IRC), was 93% with ublituximab plus ibrutinib vs 78% with ibrutinib alone (*P*=.019). The CR/CRi rate (a secondary endpoint) was 20% with ublituximab/ibrutinib vs 5% with ibrutinib alone (*P*=.024). The secondary endpoint of uMRD was achieved in 46% vs 7%, respectively (*P*<.001). IRC-assessed median PFS, another secondary endpoint, was not reached with ublituximab/ibrutinib vs 35.9 months with ibrutinib alone (HR, 0.455; 95% CI, 0.239-0.865; *P*=.016 by Cox model; Figure 9). The benefit in PFS was observed among patients with del(17p) and/or a *TP53* mutation (HR, 0.253; 95% CI, 0.099-0.646; *P*=.004 by Cox model), but not in patients with del(11q) (HR, 0.965; 95% CI, 0.357-2.607; *P*=.944 by Cox model). The study investigators noted that del(11q) is no longer categorized as a high-risk feature in CLL treated with single-agent ibrutinib.[4]

The most common adverse events of any grade were diarrhea (56%), infusion-related reaction (53%), and cough (42%). Adverse events of special interest that were more frequent with ublituximab/ibrutinib than with ibrutinib alone included atrial fibrillation (14% vs 7%) and myalgia (14% vs 24%).[4]

References

1. Le Garff-Tavernier M, Herbi L, de Romeuf C, et al. Antibody-dependent cellular cytotoxicity of the optimized anti-CD20 monoclonal antibody ublituximab on chronic lymphocytic leukemia cells with the 17p deletion. *Leukemia.* 2014;28(1):230-233.
2. Sharman JP, Farber CM, Mahadevan D, et al. Ublituximab (TG-1101), a novel glycoengineered anti-CD20 antibody, in combination with ibrutinib is safe and highly active in patients with relapsed and/or refractory chronic lymphocytic leukaemia: results of a phase 2 trial. *Br J Haematol.* 2017;176(3):412-420.
3. Sharman JP, Brander DM, Mato AR, et al. Ublituximab and ibrutinib for previously treated genetically high-risk chronic lymphocytic leukemia: results of the GENUINE phase 3 study [ASCO abstract 7504]. *J Clin Oncol.* 2017;35(15 suppl).
4. Sharman JP, Brander DM, Mato AR, et al. Effect of adding ublituximab to ibrutinib on PFS, ORR, and MRD negativity in previously treated high-risk chronic lymphocytic leukemia: final results of the GENUINE phase III study [ASCO abstract 8022]. *J Clin Oncol.* 2020;38(15 suppl).

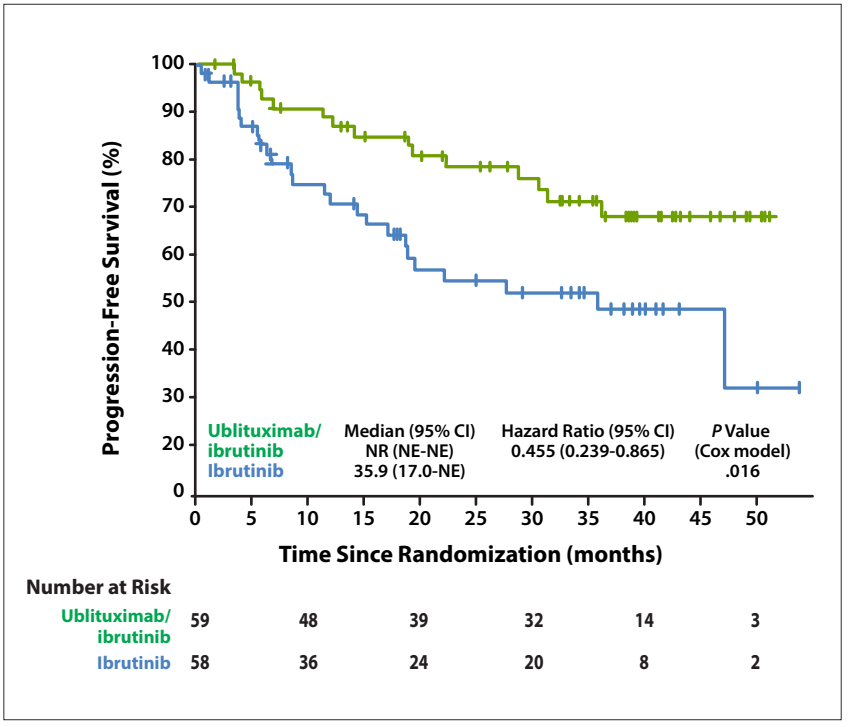

Figure 9. Progression-free survival as assessed by independent review in the phase 3 GENUINE study, an open-label, multicenter, randomized phase 3 study comparing the combination of ublituximab plus ibrutinib vs ibrutinib alone in patients with relapsed/refractory high-risk chronic lymphocytic leukemia. NE, not evaluable; NR, not reached. Adapted from Sharman JP et al. ASCO abstract 8022. *J Clin Oncol.* 2020;38(15 suppl).[4]

Clinical Activity of Cirmtuzumab, an Anti-ROR1 Antibody, in Combination With Ibrutinib: Interim Results of a Phase Ib/II Study in Mantle Cell Lymphoma or Chronic Lymphocytic Leukemia

Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is an oncogenic embryonic tyrosine kinase receptor that is expressed at high levels in many hematologic and solid cancers. Cirmtuzumab is a humanized monoclonal antibody directed against ROR1. Preclinical studies have shown that cirmtuzumab has antineoplastic activity and demonstrates synergistic activity in combination with ibrutinib.[1,2] Lee and colleagues presented interim results of a phase 1/2 study of cirmtuzumab plus ibrutinib in patients with relapsed or refractory MCL or CLL. This study was designed to evaluate the efficacy and safety of cirmtuzumab plus ibrutinib vs ibrutinib alone.[3]

Phase 1 of the study consisted of 2 parts: dose escalation (part 1), followed by cohort expansion (part 2). Phase 2 was a randomized study comparing cirmtuzumab/ibrutinib with ibrutinib alone (part 3).[3] A total of 12 patients with MCL were enrolled in part 1, and 34 patients with CLL/SLL were enrolled in parts 1 and 2. The median age of the 12 patients with MCL was 63.5 years (range, 49.0-70.0), and the median number of years since diagnosis was 2.5 years (range, <1 to 9). The median age of the 34 patients with CLL was 68.0 years (range, 37.0-86.0), and the median number of years since diagnosis was 5.5 (range, <1 to 30). Both the MCL and CLL cohorts included patients who had been heavily pretreated before study enrollment; a major proportion had undergone autologous or allogeneic stem cell transplant.[3]

The combination of cirmtuzumab plus ibrutinib was considered to be well tolerated in both patient cohorts. During phase 1, no dose-limiting or significant grade 3 toxicities possibly related to cirmtuzumab were reported. Most of the adverse events that were considered possibly related to cirmtuzumab consisted of fatigue, diarrhea, and contusion.[3]

The majority of patients were able to complete 1 year of treatment, after which they were offered enrollment in an extension study. At the April 30, 2020, data cutoff, the CR rate was 58.3% (7 of 12 patients) in the MCL cohort, and the ORR was 83.3%. In the CLL cohort, the CR rate was 3%, and the ORR was 88.2%.[3]

All of the patients in the CLL cohort benefited from treatment with cirmtuzumab plus ibrutinib. Most of these patients achieved a PR. The patients with CLL exhibited rapid tumor regression with treatment. The median PFS for patients in the CLL cohort was not reached, after a median follow-up of 12.8 months.[3]

References

1. Yu J, Chen L, Cui B, et al. Cirmtuzumab inhibits Wnt5a-induced Rac1 activation in chronic lymphocytic leukemia treated with ibrutinib. *Leukemia.* 2017;31(6):1333-1339.
2. Yu J, Chen Y, Chen L, et al. Cirmtuzumab inhibits ibrutinib-resistant, Wnt5a-induced Rac1 activation and proliferation in mantle cell lymphoma. *Oncotarget.* 2018;9(37):24731-24736.
3. Lee HJ, Choi MY, Siddiqi T, et al. Clinical activity of cirmtuzumab, an anti-ROR1 antibody, in combination with ibrutinib: interim results of a phase Ib/II study in mantle cell lymphoma (MCL) or chronic lymphocytic leukemia (CLL) [ASCO abstract 8036]. *J Clin Oncol.* 2020;38(15 suppl).

Highlights in Chronic Lymphocytic Leukemia From the 2020 American Society of Clinical Oncology Annual Meeting: Commentary

Susan M. O'Brien, MD

In 2020, the American Society of Clinical Oncology (ASCO) annual meeting presented abstracts in a virtual format. Several studies in chronic lymphocytic leukemia (CLL) provided important data for treatments such as ublituximab, acalabrutinib, venetoclax plus obinutuzumab, zanubrutinib, and chimeric antigen receptor (CAR) T-cell therapy.

Ublituximab

The GENUINE study evaluated if the addition of ublituximab, an anti-CD20, to ibrutinib would improve outcomes in patients with relapsed CLL.[1] The primary endpoint was response. Preliminary results, presented at the 2017 ASCO meeting, showed that the response rate was higher with the combination of ublituximab plus ibrutinib vs ibrutinib alone.[2] The more recent report provided data for progression-free survival (PFS).

The GENUINE trial enrolled patients with high-risk disease, defined as those with a 17p deletion, *TP53* mutation, or deletion 11q.[1] The patients had received a median of 1 prior regimen. The trial randomly assigned 62 patients to receive ibrutinib and 64

patients to treatment with ublituximab plus ibrutinib. The best overall response rate with the combination was 93%, with a 20% rate of complete response or complete response with incomplete blood count recovery. With ibrutinib alone, these rates were 78% and 5%. An impressive finding was the 46% rate of undetectable minimal residual disease (MRD) seen with combination therapy. The rate of undetectable MRD was 7% with ibrutinib alone, which was expected.

The median PFS was not reached with ublituximab plus ibrutinib vs 35.9 months with ibrutinib alone, a difference that was statistically significant (*P*=.016). However, the significance was limited to patients with the 17p deletion. Among patients with the 11q deletion, the Kaplan-Meier curves for PFS overlapped after a median follow-up of 42 months (*P*=.944).

This study is interesting for several reasons. All of the benefit accrued within the subset of patients with the 17p deletion. These are the first data to suggest that antibody therapy might be particularly beneficial in this group. The MRD undetectability rate was surprisingly high with the addition of the antibody. Another interesting observation is that the addition of ublituximab plus ibrutinib improved PFS. This finding contradicts data from 2 earlier trials using rituximab as the antibody: one from MD Anderson that evaluated ibrutinib with or without rituximab in relapsed CLL, and the Alliance trial that compared bendamustine plus rituximab vs ibrutinib vs ibrutinib plus rituximab in the frontline setting.[3,4] These trials clearly showed that adding rituximab to ibrutinib did not impact PFS. (There was possibly a slight improvement in the response rate.) In the Alliance trial, both ibrutinib arms had longer PFS than bendamustine plus rituximab, but the addition of rituximab to ibrutinib did not improve outcome.

The improvement in PFS observed in the GENUINE study may be attributable to the specific antibody: ublituximab rather than ibrutinib. However, another distinction between the GENUINE trial and earlier trials that combined a small molecule with an antibody concerns the length of therapy. In the GENUINE trial, the antibody was continued indefinitely with maintenance therapy, rather than stopped after 6 months. Therefore, patients received ublituximab every 3 months for long periods. It is not known whether the improvement in PFS seen with combination therapy in the GENUINE trial is attributable to the specific antibody or to the continued use of antibody therapy.

Acalabrutinib

Dr Richard Furman and colleagues presented results of a pooled safety analysis of monotherapy with acalabrutinib, a second-generation Bruton tyrosine kinase (BTK) inhibitor.[5] Acalabrutinib is approved for the treatment of CLL or small lymphocytic leukemia, as well as for patients with mantle cell lymphoma who have received at least 1 prior treatment. Acalabrutinib has a higher half maximal inhibitory concentration (IC_{50}) for some of the other kinases targeted by ibrutinib, in addition to BTK.[6] It is thought that many of the adverse events associated with ibrutinib are related to kinases other than BTK.[7] Acalabrutinib was designed to cause fewer side effects than ibrutinib.[8]

The data in this safety analysis were drawn from multiple clinical trials and included more than 1000 patients with a variety of lymphoid malignancies, including CLL. The median duration of follow-up was 26 months.

The analysis showed that acalabrutinib is a very safe drug. The most common side effect is headache, which occurs early. Patients often developed tachyphylaxis to headache. The median onset of headache was 20 days into therapy, but most cases resolved and did not recur. Toxicities of particular interest for BTK inhibitors include atrial fibrillation and hypertension. This pooled analysis reported rates of 4.4% for atrial fibrillation and 7.6% for hypertension, confirming findings from earlier studies. Trials of ibrutinib report higher rates of cardiovascular side effects.[9,10] Only 9% of patients discontinued acalabrutinib owing to adverse events. In comparison, most trials of ibrutinib report a discontinuation rate of approximately 20%.[9,10] In conclusion, this large safety analysis confirmed that acalabrutinib appears to have less cardiovascular toxicity and may be better tolerated—with fewer discontinuations for adverse events—compared with ibrutinib.

Dr Paolo Ghia and colleagues presented final results of ASCEND, an important phase 3 trial that, along with the ELEVATE trial, helped lead to the approval of acalabrutinib in patients with CLL.[11,12] The results from this trial were recently published.[11] This 3-armed, randomized trial enrolled patients with relapsed/refractory CLL. The trial randomly assigned 310 patients to treatment with acalabrutinib at 100 mg twice daily (the standard dose) or a control arm: idelalisib plus rituximab (at the standard doses) or bendamustine plus rituximab. For patients in the control group, the investigators selected the treatment.

The primary endpoint of PFS was significantly longer with acalabrutinib. The estimated 18-month PFS rates were 82% with acalabrutinib vs 48% in the control arms. The median PFS was not reached in the acalabrutinib arm, compared with 18.6 months with bendamustine plus rituximab and 16.2 months with idelalisib plus rituximab. The median overall survival was not reached in any of the arms. However, more than 80% of the patients were still alive at the time of the analysis.

The rate of atrial fibrillation was 6% with acalabrutinib vs 3% in the control arms, and the rate of hypertension was 5% vs 4%, respectively. Aca-

labrutinib was generally well-tolerated, and patients were able to continue treatment. Oddly, this report provides the final data for this study, at a median follow-up of only 22 months.

Venetoclax

The randomized phase 3 CLL14 trial led the US Food and Drug Administration (FDA) to approve venetoclax and obinutuzumab as frontline therapy for CLL.[13] Results were updated at the 2020 ASCO meeting.[14] This important German trial enrolled more than 400 treatment-naive patients. The patients were randomly assigned to treatment with either chlorambucil and obinutuzumab (n=216) or venetoclax and obinutuzumab (n=216). In both arms, obinutuzumab was front-loaded and stopped after 6 months. Then, treatment with venetoclax or chlorambucil was given for 12 months. Therefore, both regimens were time-limited and administered for 1 year.

The presentation at the ASCO meeting provided data for a median follow-up of 39.5 months. There was a dramatic difference in the primary endpoint of PFS. The rate of PFS was 81.9% in the venetoclax/obinutuzumab arm vs 49.5% in the chlorambucil/obinutuzumab arm. The rate of PFS seen with chlorambucil/obinutuzumab was higher than in other studies, which tend to administer chlorambucil for 6 months, rather than 12 months.[15] The median overall survival was not reached in either arm, but more than 90% of patients were alive at the time of the analysis.

All patient subgroups benefited from obinutuzumab and venetoclax. The data show that patients with the 17p deletion are still a high-risk group. Among patients with the 17p deletion, outcome was better with venetoclax/obinutuzumab vs chlorambucil/obinutuzumab. This finding is not surprising because it is known that patients with the 17p deletion do not respond well to chemotherapy and should not receive it.[16] Among patients treated with venetoclax plus obinutuzumab, the median PFS had not been reached. However, according to Kaplan-Meier analysis, outcome appears to be much better among patients without the 17p deletion.

Another interesting observation emerging from these data is that the duration of PFS associated with venetoclax may differ according to immunoglobulin heavy chain gene (*IGHV*) mutation status. Patients with the *IGHV* mutation may have a slightly better outcome, although the difference did not reach statistical significance at the time of the report. It will be interesting to see how these data evolve in future analyses. In contrast, there have been no differences in PFS between patients with or without the *IGHV* mutation when treated with BTK inhibitors. The longest follow-up for ibrutinib is 8 years, and there is no difference in PFS based on *IGHV* mutation status.[17] As expected, there was a substantial difference in outcome according to *IGHV* mutation status in the chemotherapy arm. Historically, with chemotherapy-based therapy, the *IGHV* mutation status has a substantial impact on PFS.[18]

Patients treated with venetoclax must be monitored for tumor lysis syndrome,[19] and this toxicity was reported in the CLL14 trial. It is also important to remain alert for neutropenia, which can be caused by both venetoclax and the antibody. Significant neutropenia can be managed with periodic use of growth factor support or by reducing the dose. Some preliminary data suggest that it is possible to reduce the dose of venetoclax and still maintain prolonged remissions.[20]

At the end of treatment with venetoclax plus obinutuzumab, undetectable MRD was reported in 75% of patients. An impressive finding is that at 18 months after treatment completion, MRD was undetectable in 47% of patients in this arm.

The median PFS was not reached with venetoclax plus obinutuzumab vs 35.6 months with chlorambucil plus obinutuzumab. Patients who developed undetectable MRD appeared to have the longest PFS, which is not surprising. The benefit of MRD undetectability was the same regardless of whether the patient had a complete response or a partial response. In most cases, a partial response was defined by the presence of small residual nodes. These data reflect a trend observed with the small-molecule therapies: MRD status trumps response status (as measured with standard criteria from the National Cancer Institute). However, among patients with detectable MRD, PFS is longer in those with a standard complete response vs a partial response.

The remissions were durable, and few relapses were reported. There was no median PFS after follow-up of approximately 3 years—which was 2 years after completion of study treatment. When patients do relapse, there is hope that it might be possible to use the same drug again because the relapse will occur during a treatment-free period, and the lack of continued treatment will not drive a resistant clone.

Zanubrutinib

A trial from Memorial Sloan Kettering Cancer Center evaluated a 3-drug combination of zanubrutinib, obinutuzumab, and venetoclax with the goal of establishing another finite therapy in frontline CLL.[21] Zanubrutinib is a second-generation BTK inhibitor. Like acalabrutinib, zanubrutinib was designed to be more potent than ibrutinib and to have fewer side effects, with less off-target kinase inhibition. The FDA has not yet approved zanubrutinib for CLL, but it is approved for mantle cell lymphoma.

Two previous trials have evaluated combination therapy with small molecules in CLL. An investigator-initiated trial at MD Anderson Cancer Center evaluated ibrutinib and venetoclax, and data were published in

2019.[22] This regimen was also studied in the CAPTIVATE trial, which has been presented at several meetings (although not yet published).[23] The data from both of these studies were similar, showing that 72% to 75% of patients achieved undetectable MRD in the bone marrow as a best response. The high rate of MRD undetectability is allowing patients to stop therapy.

The trial from Memorial Sloan Kettering Cancer Center employed a strategy in which the patients received a 2-month lead-in with zanubrutinib (at the standard dose of 160 twice daily) and obinutuzumab. The CAPTIVATE trial and the MD Anderson trial also used a lead-in with ibrutinib.[22,23] The idea behind the lead-in treatment is to debulk the patients, thereby reducing the risk for tumor lysis when they receive venetoclax.

Patients completed 8 total cycles of obinutuzumab and 6 cycles of the triplet combination, and then underwent MRD assessment. MRD was first measured in the peripheral blood. A subsequent bone marrow test was administered only if the peripheral blood test was negative. A negative bone marrow test triggered a computerized axial tomography (CAT) scan to assess the response (according to criteria from the International Workshop on Chronic Lymphocytic Leukemia). Patients with undetectable MRD confirmed in the bone marrow received 2 additional cycles of therapy. If their next peripheral blood MRD test showed undetectability, they could stop therapy.

The trial enrolled 39 patients, with a short median follow-up of 11 months.[21] CLL International Prognostic Index scores indicated high risk or very high risk disease in 72%, an unusually high rate for the frontline setting. At screening, 43% of patients had a high risk of tumor lysis. At the time of venetoclax initiation—after the 2-month lead-in with zanubrutinib and the antibody—risk remained high in only 5%. As in the CAPTIVATE trial and the study from MD Anderson,[22,23] this trial significantly reduced tumor lysis risk with the lead-in treatment. At the time of the report, no patients in the trial had developed laboratory or clinical tumor lysis. At a median follow-up of 11 months, the rate of MRD undetectability was 84% in the blood and 73% in the bone marrow. Thus, the rate of bone marrow MRD undetectability was similar to that seen in the CAPTIVATE trial and the trial from MD Anderson.[22,23]

The results of this trial raise an interesting question regarding how much the antibody adds to the small-molecule combination. With an MRD undetectability rate ranging from 70% to 80%, a very large trial would be required to detect an improvement from the antibody (and this study was not designed to do so). It is too early to discern the impact of the antibody. Interestingly, among the patients who had discontinued therapy based on undetectable MRD, 52% were in a complete response and 43% were in a partial response (as defined, in most cases, by persistent, borderline-size lymph nodes). As alluded to in the earlier discussion of the CLL14 trial,[14] these small lymph nodes may not represent residual disease.

Unsurprisingly, the main toxicities reported with the regimen of zanubrutinib, obinutuzumab, and venetoclax were hematologic.[21] Neutropenia was the most frequent treatment-emergent adverse event; most cases were grade 1 or 2. Venetoclax and obinutuzumab are each known to cause significant neutropenia.[24,25] In this study, the rate of infection was low. Hypertension occurred in 5% of patients. The rate of atrial fibrillation was 2.6%. Data from other studies suggest that zanubrutinib might have the lowest numerical incidence of atrial fibrillation among the BTK inhibitors.[26]

CAR T-Cell Therapy

Dr Kathryn Cappell and colleagues presented a long-term follow-up analysis of a study from the National Cancer Institute evaluating CAR T-cell therapy in patients with B-cell lymphoma or CLL.[27] Most trials of CAR T-cell therapy tend to present early data on response rates and toxicity. Although early data are important, they do not address the number of patients who are potentially cured with this strategy. It is known that CAR T-cell therapy can cure some patients, particularly those with acute lymphocytic leukemia. There are studies in the pediatric acute lymphocytic leukemia setting with follow-up of several years.[28] However, many of these patients receive consolidation therapy, such as transplant.

Under Dr James Kochenderfer, the National Cancer Institute was among the first institutions to study CAR T-cell therapy.[29] The original trial divided patients into different cohorts, depending on the lymphodepletion technique and other factors. The study enrolled 3 different populations: 28 patients with diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma, 8 patients with low-grade lymphoma, and 7 patients with CLL. The patients with CLL were very heavily pretreated. Among all the disease cohorts, the median number of prior regimens was 4. Among patients with diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma, 68% were refractory to chemotherapy. The patients in this study represented a group at very high risk.

The overall response rate was approximately 80%, with complete responses in 58% and partial responses in 23%. Data across all CAR T-cell therapies suggest that partial responses are not durable. This study also confirmed data from earlier trials showing that higher peak CAR T-cell levels are associated with response and duration of response.[30]

Among the 25 patients with a complete response, 60% of these responses were ongoing at the time of the report. The duration of response for ongoing complete responses was

impressive, ranging from 43 months to 113 months. The median event-free survival was 55 months, and the median overall survival was not reached. Twenty-four patients with a complete response were evaluable for B-cell and immunoglobulin levels. Nine of these patients (38%) never recovered their B cells, and 75% had an abnormality consisting of a low level of at least 1 immunoglobulin. Interestingly, 15 patients recovered B cells, although this development did not indicate lymphoma relapse. At the time of the report, 10 of 15 patients (67%) remained in a complete response, with a median time since B-cell recovery of 50 months.

The study did not specify whether patients received treatment after CAR T-cell therapy. Patients in the enrolled population are not usually treated with allogeneic transplant, and it seems likely that the patients in this study did not receive consolidation therapy. Therefore, the data from this analysis are impressive, suggesting that there is a cure fraction with CAR T-cell therapy in lymphoma patients, who—as shown in this study—can have very refractory disease.

Disclosure

Dr O'Brien is a consultant for Amgen, Astellas, Celgene, GlaxoSmithKline, Janssen Oncology, Aptose Biosciences Inc, Vaniam Group LLC, AbbVie, Alexion, Verastem, Eisai, Juno Therapeutics, and Vida Ventures. She has received research support from Kite, Regeneron, and Acerta. She is a consultant and/or has received research support from Gilead, Pharmacyclics, TG Therapeutics, Pfizer, and Sunesis.

References

1. Sharman JP, Brander DM, Mato AR, et al. Effect of adding ublituximab to ibrutinib on PFS, ORR, and MRD negativity in previously treated high-risk chronic lymphocytic leukemia: final results of the GENUINE phase III study [ASCO abstract 8022]. *J Clin Oncol.* 2020;38(15 suppl).
2. Sharman JP, Brander DM, Mato AR, et al. Ublituximab and ibrutinib for previously treated genetically high-risk chronic lymphocytic leukemia: results of the GENUINE phase 3 study [ASCO abstract 7504]. *J Clin Oncol.* 2017;35(15 suppl).
3. Burger JA, Sivina M, Jain N, et al. Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. *Blood.* 2019;133(10):1011-1019.
4. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med.* 2018;379(26):2517-2528.
5. Furman RR, Byrd JC, Owen RG, et al. Safety of acalabrutinib monotherapy in hematologic malignancies: pooled analysis from clinical trials [ASCO abstract 8064]. *J Clin Oncol.* 2020;38(15 suppl).
6. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): a covalent Bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. *J Pharmacol Exp Ther.* 2017;363(2):240-252.
7. Aguilar C. Ibrutinib-related bleeding: pathogenesis, clinical implications and management. *Blood Coagul Fibrinolysis.* 2018;29(6):481-487.
8. Bye AP, Unsworth AJ, Desborough MJ, et al. Severe platelet dysfunction in NHL patients receiving ibrutinib is absent in patients receiving acalabrutinib. *Blood Adv.* 2017;1(26):2610-2623.
9. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol.* 2019;94(12):1353-1363.
10. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia.* 2020;34(3):787-798.
11. Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia [published online May 27, 2020]. *J Clin Oncol.* doi:10.1200/JCO.19.03355.
12. Ghia P, Pluta A, Wach M, et al. Acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed/refractory chronic lymphocytic leukemia: ASCEND final results [ASCO abstract 8015]. *J Clin Oncol.* 2020;38(15 suppl).
13. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med.* 2019;380(23):2225-2236.
14. Al-Sawaf O, Zhang C, Tandon M, et al. Fixed-duration venetoclax-obinutuzumab for previously untreated patients with chronic lymphocytic leukemia: follow-up of efficacy and safety results from the multicenter, open-label, randomized, phase III CLL14 trial [ASCO abstract 8027]. *J Clin Oncol.* 2020;38(15 suppl).
15. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med.* 2014;370(12):1101-1110.
16. Hallek M, Fischer K, Fingerle-Rowson G, et al; International Group of Investigators; German Chronic Lymphocytic Leukaemia Study Group. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet.* 2010;376:1164-1174.
17. Byrd JC, Furman RR, Coutre SE, et al. Ibrutinib treatment for first-line and relapsed/refractory chronic lymphocytic leukemia: final analysis of the pivotal phase Ib/II PCYC-1102 study [published online March 24, 2020]. *Clin Cancer Res.* doi:10.1158/1078-0432.CCR-19-2856.
18. Kutsch N, Bahlo J, Robrecht S, et al. Long term follow-up data and health-related quality of life in frontline therapy of fit patients treated with FCR versus BR (CLL10 trial of the GCLLSG). *Hemasphere.* 2020;4(1):e336. doi:10.1097/HS9.0000000000000336.
19. Koehler AB, Leung N, Call TG, et al. Incidence and risk of tumor lysis syndrome in patients with relapsed chronic lymphocytic leukemia (CLL) treated with venetoclax in routine clinical practice [published online May 25, 2020]. *Leuk Lymphoma.* doi:10.1080/10428194.2020.1768384.
20. Mato AR, Sharman J, Biondo JML, et al. Impact of premature venetoclax (ven) discontinuation/interruption on outcomes in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): phase III MURANO study results [ASCO abstract P361]. *J Clin Oncol.* 2020;38(15 suppl).
21. Soumerai JD, Mato AR, Carter J, et al. Initial results of a multicenter, investigator initiated study of MRD driven time limited therapy with zanubrutinib, obinutuzumab, and venetoclax [ASCO abstract 8006]. *J Clin Oncol.* 2020;38(15 suppl).
22. Jain N, Keating M, Thompson P, et al. Ibrutinib and venetoclax for first-line treatment of CLL. *N Engl J Med.* 2019;380(22):2095-2103.
23. Tam CS, Siddiqi T, Allan JN, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): results from the MRD cohort of the phase II CAPTIVATE study [ASH abstract 35]. *Blood.* 2019;134(suppl 1).
24. Mato AR, Thompson M, Allan JN, et al. Real-world outcomes and management strategies for venetoclax-treated chronic lymphocytic leukemia patients in the United States. *Haematologica.* 2018;103(9):1511-1517.
25. Leblond V, Aktan M, Ferra Coll CM, et al. Safety of obinutuzumab alone or combined with chemotherapy for previously untreated or relapsed/refractory chronic lymphocytic leukemia in the phase IIIb GREEN study. *Haematologica.* 2018;103(11):1889-1898.
26. Tam CSL, Opat S, D'Sa S, et al. ASPEN: results of a phase III randomized trial of zanubrutinib versus ibrutinib for patients with Waldenström macroglobulinemia (WM) [ASCO abstract 8007]. *J Clin Oncol.* 2020;38(15 suppl).
27. Cappell KM, Sherry RM, Yang JC, et al. Long-term follow-up of anti-CD19 CAR T-cell therapy for B-cell lymphoma and chronic lymphocytic leukemia [ASCO abstract 3012]. *J Clin Oncol.* 2020;38(15 suppl).
28. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med.* 2018;378(5):439-448.
29. Kochenderfer JN, Wilson WH, Janik JE, et al. Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. *Blood.* 2010;116(20):4099-4102.
30. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol.* 2019;20(1):31-42.

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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CLL=chronic lymphocytic leukemia.
BTKi=Bruton tyrosine kinase inhibitor.

CALQUENCE®
(acalabrutinib) 100 mg capsules

Indication and Usage

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

Select Safety Information

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

Please see Brief Summary of Prescribing Information on adjacent pages.

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