

A SPECIAL MEETING REVIEW EDITION

Highlights in Chronic Lymphocytic Leukemia From the 2021 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2021 ASCO Annual Meeting

• June 4-8, 2021

Special Reporting on:

- First Results of a Head-to-Head Trial of Acalabrutinib vs Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia
- Fixed-Duration First-Line Treatment With Ibrutinib Plus Venetoclax for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Primary Analysis of the Fixed-Duration Cohort of the Phase 2 CAPTIVATE Study
- Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: ELEVATE-TN 4-Year Follow-Up
- Up to Seven Years of Follow-Up in the RESONATE-2 Study of First-Line Ibrutinib Treatment for Patients With Chronic Lymphocytic Leukemia
- First-in-Human Study of Lisoftoclax (APG-2575), a Novel BCL-2 Inhibitor, in Patients With Relapsed/Refractory CLL and Other Hematologic Malignancies
- Survival Trends in Chronic Lymphocytic Leukemia in the Era of Oral Targeted Therapies in the United States: SEER Database Analyses (1985 to 2017)
- Identification of Genetic Markers Associated With Ibrutinib-Related Cardiovascular Toxicity
- Phase 1/2 Study of Cirmtuzumab and Ibrutinib in Mantle Cell Lymphoma or Chronic Lymphocytic Leukemia

PLUS Meeting Abstract Summaries

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First Results of a Head-to-Head Trial of Acalabrutinib vs Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia

Ibrutinib was the first irreversible Bruton's tyrosine kinase (BTK) inhibitor to receive approval from the US Food and Drug Administration (FDA) for the treatment of adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).¹ In addition to binding to BTK, ibrutinib also binds to non-BTK kinases, which may contribute to the adverse events (AEs) associated with this therapy.²⁻⁵ Cardiovascular toxicities and other AEs have led some patients to discontinue ibrutinib.⁶⁻⁸ Acalabrutinib is a next-generation, irreversible BTK inhibitor that was selected for a reduction in off-target binding activity.⁹ Acalabrutinib is approved by the FDA for the treatment of patients with CLL or SLL. Acalabrutinib also received accelerated approval for patients with mantle cell lymphoma treated with at least 1 prior therapy.

The phase 3 ELEVATE-RR trial compared acalabrutinib (100 mg, twice daily) vs ibrutinib (420 mg, once daily)

in patients with previously treated CLL requiring therapy.^{8,10,11} This open-label trial included 533 patients with deletion 17p (del[17p]) or deletion 11q (del[11q]) based on central laboratory testing. Patients with significant cardiovascular disease were excluded. Prior to randomization, the patients were stratified based on del(17p) status, Eastern Cooperative Oncology Group (ECOG) performance status, and the number of prior therapies. The primary endpoint was noninferiority based on progression-free survival (PFS) as determined by an independent review committee. Key secondary endpoints included the incidence of any-grade atrial fibrillation/flutter and the incidence of grade 3 or higher infection.

The baseline characteristics were well balanced between the 2 arms.¹¹ The patients' median age was 66 years, and 16% were ages 75 years or older. Bulky disease (>5 cm) was observed in 48% to 51% of patients in the 2 arms, and approximately half of patients

had Rai stage III/IV disease. High-risk cytogenetic features included del(17p) (in 45% of patients in both arms), del(11q) (in 62% of the acalabrutinib arm vs 66% of the ibrutinib arm), complex karyotype (in 46% vs 47%), mutated *TP53* (in 37% vs 42%), and an unmutated immunoglobulin heavy chain variable region gene (*IGHV*) (in 82% vs 89%). The patients had received a median of 2 prior therapies (range, 1-12). The median follow-up was 41 months (range, 0.0-59.1 months).

Overall, the rate of treatment discontinuation was 52.6% in the acalabrutinib arm vs 58.5% in the ibrutinib arm. Discontinuation owing to disease progression was reported in 30.6% of the acalabrutinib arm vs 25.7% of the ibrutinib arm. Adverse events (AEs) led to treatment discontinuation in 14.9% vs 22.3%, respectively.

The trial met its primary endpoint of noninferiority, with a median PFS of 38.4% in both treatment arms (hazard ratio [HR], 1.00; 95% CI, 0.79-1.27;

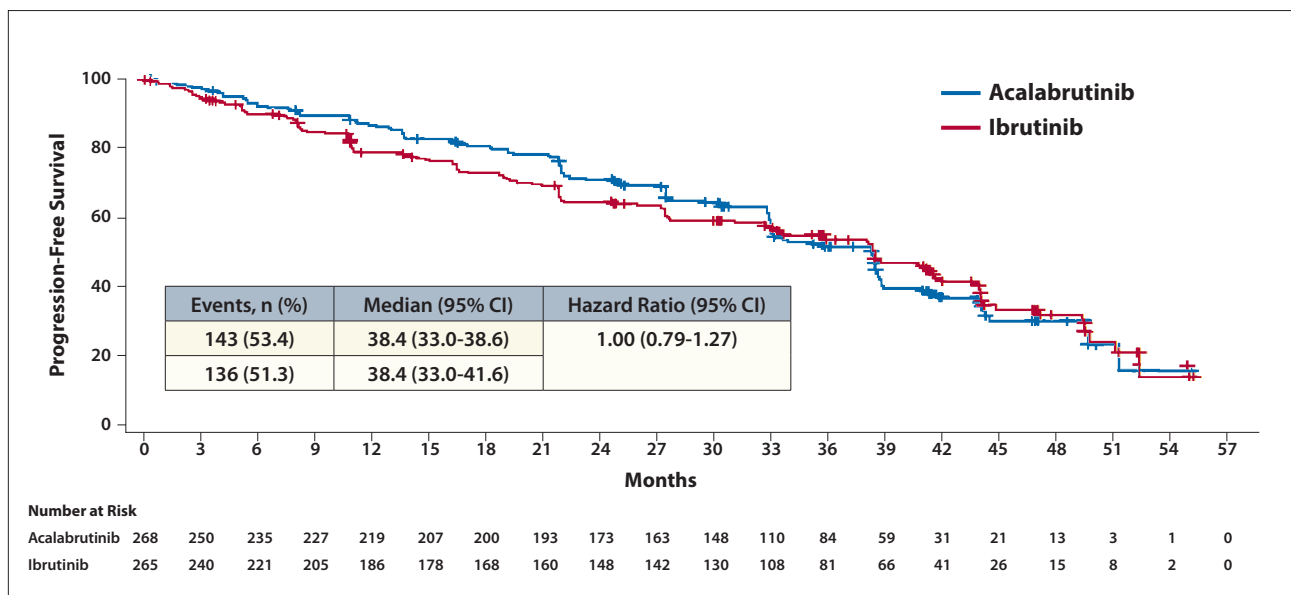


Figure 1. Progression-free survival as assessed by an independent review committee in the phase 3 ELEVATE-RR trial, which compared acalabrutinib vs ibrutinib in patients with previously treated chronic lymphocytic leukemia. Adapted from Byrd JC et al. ASCO abstract 7500. *J Clin Oncol.* 2021;39(15 suppl).¹¹

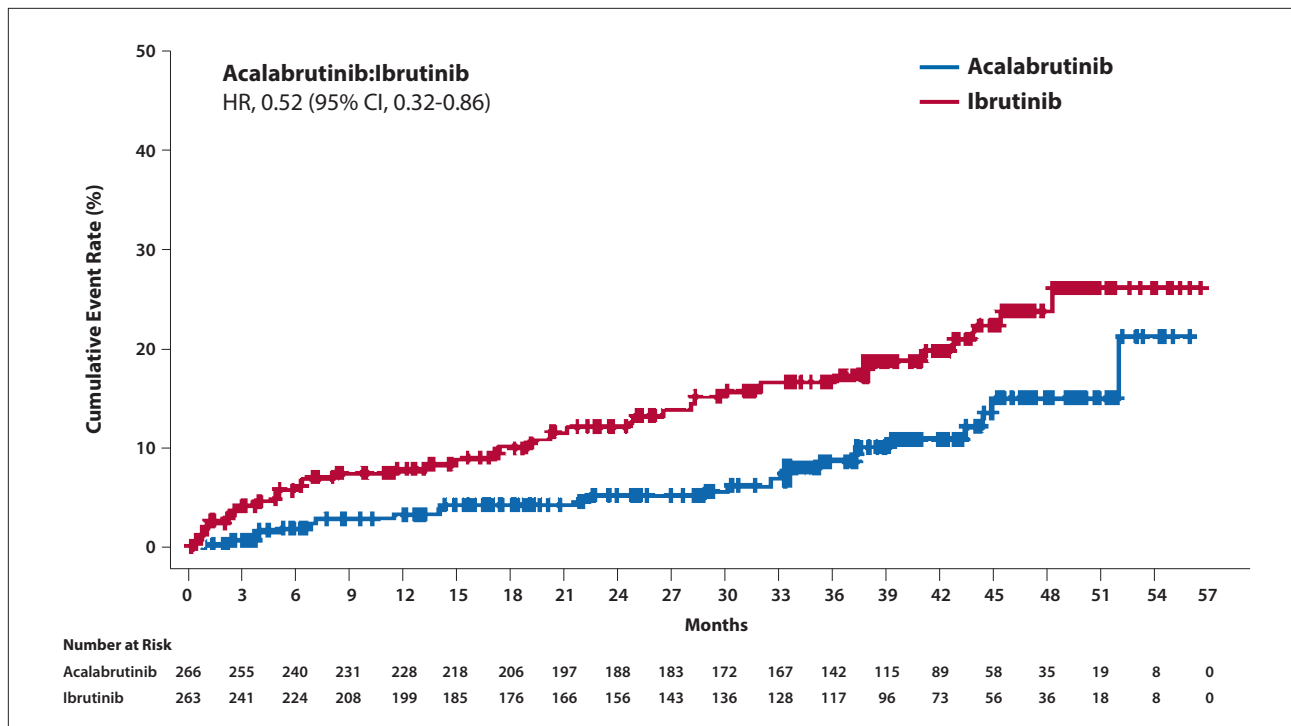


Figure 2. The lower cumulative incidence of any-grade atrial fibrillation/flutter among patients with previously treated chronic lymphocytic leukemia who received acalabrutinib vs ibrutinib in the phase 3 ELEVATE-RR trial. HR, hazard ratio. Adapted from Byrd JC et al. ASCO abstract 7500. *J Clin Oncol.* 2021;39(15 suppl).¹¹

Figure 1).¹¹ A prespecified analysis showed similar PFS rates across all subgroups, including those based on age, sex, ECOG performance status, bulky disease, number of prior therapies, and high-risk genetic features.

Any-grade atrial fibrillation/flutter was reported in 9.4% of the acalabrutinib arm vs 16.0% of the ibrutinib arm ($P=.02$). The number of events per 100 person-months was 0.366 in the acalabrutinib arm vs 0.721 in the ibrutinib arm. The median time to onset of atrial fibrillation/flutter was 28.8 months (range, 0.4-52.0 months) with acalabrutinib vs 16.0 months (range, 0.5-48.3 months) with ibrutinib. No patients in the acalabrutinib arm discontinued treatment owing to atrial fibrillation/flutter vs 16.7% in the ibrutinib arm. Grade 3 or higher infection occurred in 30.8% of the acalabrutinib arm vs 30.0% of the ibrutinib arm ($P=.8777$). Richter transformation was reported in 3.8% vs 4.9%, respectively. The median

overall survival (OS) was not reached in either arm, with an HR of 0.82 (95% CI, 0.59-1.15) favoring acalabrutinib.

The median duration of treatment was 38.3 months (range, 0.3-55.9 months) in the acalabrutinib arm vs 35.5 months (range, 0.2-57.7 months) in the ibrutinib arm.¹¹ AEs of grade 3 or higher were reported in 68.8% of the acalabrutinib arm vs 74.9% of the ibrutinib arm. AEs leading to treatment discontinuation occurred in 14.7% vs 21.3%, respectively. Serious AEs occurred in 53.8% vs 58.6%. Deaths from AEs were reported in 6.4% of the acalabrutinib arm vs 9.5% of the ibrutinib arm. The most common AEs of any grade that were significantly more common in either the acalabrutinib or the ibrutinib arm included diarrhea (34.6% vs 46.0%), headache (34.6% vs 20.2%), and cough (28.9% vs 21.3%). Grade 3 or higher AEs of interest that were significantly more common in the ibrutinib arm included diarrhea (1.1%

vs 4.9%) and hypertension (4.1% vs 8.7%). Grade 3 or higher AEs of interest that were significantly more common in the acalabrutinib arm included headache (1.5% vs 0%) and fatigue (3.4% vs 0%). The cumulative incidences of several any-grade AEs were lower with acalabrutinib, including atrial fibrillation/flutter (HR, 0.52; 95% CI, 0.32-0.86; Figure 2), hypertension (HR, 0.34; 95% CI, 0.21-0.54), bleeding events (HR, 0.63; 95% CI, 0.49-0.82), diarrhea (HR, 0.61; 95% CI, 0.46-0.80), and arthralgia (HR, 0.61; 95% CI, 0.41-0.90). In summary, acalabrutinib had similar efficacy and was better tolerated than ibrutinib in patients with previously treated CLL.

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Fixed-Duration First-Line Treatment With Ibrutinib Plus Venetoclax for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Primary Analysis of the Fixed-Duration Cohort of the Phase 2 CAPTIVATE Study

The BTK inhibitor ibrutinib is the only targeted therapy that has yielded a significant improvement in OS in phase 3 studies of patients with previously untreated CLL.^{1,2} Venetoclax inhibits the activity of BCL-2.³ It is FDA-approved for the treatment of CLL, alone or in combination with an anti-CD20 antibody, and has achieved high rates of undetectable minimal residual disease (MRD). The synergistic killing activity of ibrutinib plus venetoclax in CLL cells can be attributed to their ability to eliminate distinct CLL cell subpopulations.⁴

The combination of ibrutinib plus venetoclax was evaluated as first-line treatment for CLL in the international phase 2 CAPTIVATE study.⁵ The trial enrolled patients ages 70 years or older who had active disease requiring treatment based on International Workshop on CLL (iwCLL) criteria.⁶ All patients received 3 cycles of lead-in ibrutinib followed by 12 cycles of ibrutinib plus venetoclax. The MRD cohort was evaluated after 12 cycles of combination therapy and, based on undetectable MRD status, patients were then randomly assigned to further treatment with placebo, ibrutinib monotherapy, or ibrutinib plus venetoclax.⁵ This strategy yielded undetectable MRD in more than two-thirds of patients. The 30-month PFS rates were 95% or higher in all of the MRD-guided treatment groups.

The fixed-dose cohort of patients

in the CAPTIVATE study received 3 cycles of ibrutinib lead-in therapy followed by 12 cycles of ibrutinib plus venetoclax, with no further treatment.⁷ Ibrutinib was administered at 420 mg once daily. Venetoclax was ramped up over 5 weeks to 400 mg once daily. The primary endpoint was the rate of complete response (CR)/CR with incomplete bone marrow recovery in patients without del(17p), and the study was powered to exclude a minimum CR rate of 37%. Among 159 enrolled patients,

147 (92%) completed 12 cycles of combination therapy. The median treatment duration was 13.8 months (range, 0.5-24.9 months), or 15 cycles of 28 days each, and the median follow-up was 14.0 months. The 159 patients were a median age of 60 years (range, 33-71 years) and 28% had Rai stage III/IV disease. High-risk features included unmutated *IGHV* (in 56%), complex karyotype (in 19%), del(11q) (in 18%), del(17p)/*TP53* mutation (in 17%), and del(17p) (in 13%). Thirty percent of

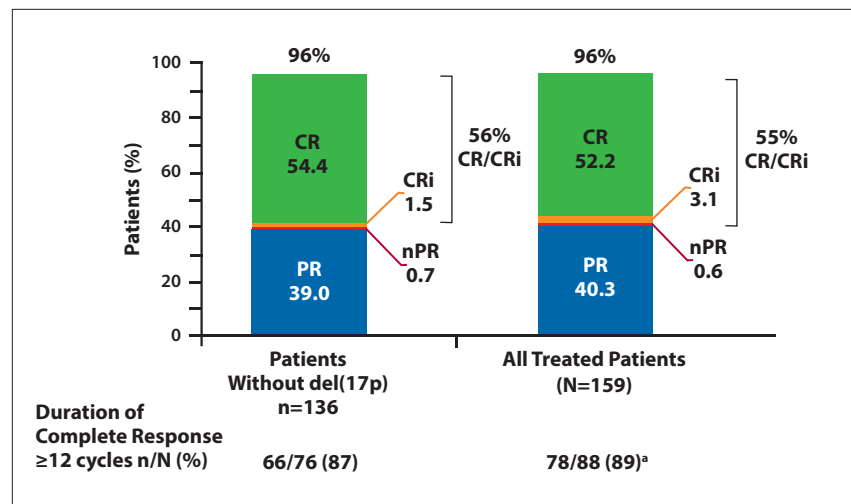


Figure 3. The best overall response rate among patients with previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma who received fixed-duration treatment with ibrutinib plus venetoclax in the phase 2 CAPTIVATE study. ^aAfter achieving a complete response, 9 patients with less than 1 year of follow-up were not evaluable. One patient died 7 months after CR and completion of therapy. CR, complete response; CRi, complete response with incomplete bone marrow recovery; del(17p), deletion 17p; nPR, nodular partial response; PR, partial response. Adapted from Ghia P et al. ASCO abstract 7501. *J Clin Oncol*. 2021;39(15 suppl).⁷

patients had at least 1 lymph node with a diameter of 5 cm or more.

The study met its primary endpoint, with a CR rate of 56% (95% CI, 48%-64%) in patients without del(17p) ($P < .0001$; Figure 3).⁷ The overall response rate (ORR) in patients without del(17p) was 96%. Among all treated patients, the ORR was also 96%, with a slightly lower CR rate of 52%. These results compare favorably with those from the CLL10 trial, which reported a CR rate of 40% with fludarabine, cyclophosphamide, and rituximab.⁸ The ORR was similar across most high-risk subgroups; however, patients with bulky disease had a CR rate of 31% (95% CI, 18%-44%). Among patients without del(17p), the rate of undetectable MRD was 76% in the peripheral blood and 62% in the bone marrow. The entire study population had similar rates of undetectable MRD (77% in the peripheral blood and 60% in the bone marrow). The 24-month PFS rate was 96% among patients without del(17p) and 95% in the overall study population of 159 patients. The 24-month OS rate was 98% for both cohorts. Among 27 patients with del(17p), the ORR was 96%, including a CR rate of 52%. The estimated 24-month PFS was 84%, and the estimated 24-month OS was 96%.

Most AEs were grade 1/2. The most common grade 3/4 AEs were neutropenia (33%), infections (8%), and hypertension (6%). One fatal AE occurred.

Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: ELEVATE-TN 4-Year Follow-Up

Acalabrutinib is a second-generation, covalent inhibitor of BTK. The phase 3 ELEVATE-TN study compared acalabrutinib, with or without obinutuzumab, vs obinutuzumab plus chlorambucil in patients with CLL or SLL.^{1,2} The study enrolled patients ages 65 years and

ABSTRACT SUMMARY Association Between Baseline Geriatric Domains and Survival in Older Adults With Chronic Lymphocytic Leukemia

A retrospective study examined the relationship between baseline geriatric domains and survival of elderly patients with CLL (Abstract 12041). The study analyzed data from 369 patients, ages 65 years or older, who had received either bendamustine plus rituximab, ibrutinib plus rituximab, or ibrutinib monotherapy in a phase 3 trial. Baseline geriatric domain impairments included a Timed Up and Go test result of longer than 10 seconds (51.7%), more than 5% weight loss in the prior 6 months (22.5%), impaired activities of daily living (ADLs; 21.0%), 1 or more falls in the prior 6 months (12.9%), body mass index below 22 kg/m² (8.4%), and cognitive impairment (3.8%). Geriatric domains that were significantly associated with OS included impairment as indicated by the ADL score (HR, 0.67; $P = .012$), the instrumental ADL score (HR, 0.98; $P = .007$), and the social activity score (HR, 0.97; $P = .004$), as well as more than 5% weight loss in the prior 6 months (HR, 2.58; $P = .008$). The same impaired geriatric domains were significantly associated with PFS: ADL score (HR, 0.77; $P = .028$), instrumental ADL score (HR, 0.99; $P = .007$), social activity score (HR, 0.97; $P < .001$), and more than 5% weight loss during the prior 6 months (HR, 2.87; $P < .001$).

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older, as well as younger adults with comorbidities, including a creatinine clearance of 30 mL/min to 69 mL/min and a Cumulative Illness Rating Scale–Geriatric score above 6. All patients had previously untreated CLL/SLL requiring treatment per 2008 iwCLL criteria and an ECOG performance

status of at least 2.³ The primary endpoint was PFS.

The trial randomly assigned 535 patients into the 3 treatment arms. Across the arms, the patients' median age was 70 to 71 years. Bulky disease was present in 26% to 38% of patients, and 21% to 29% of patients had Rai

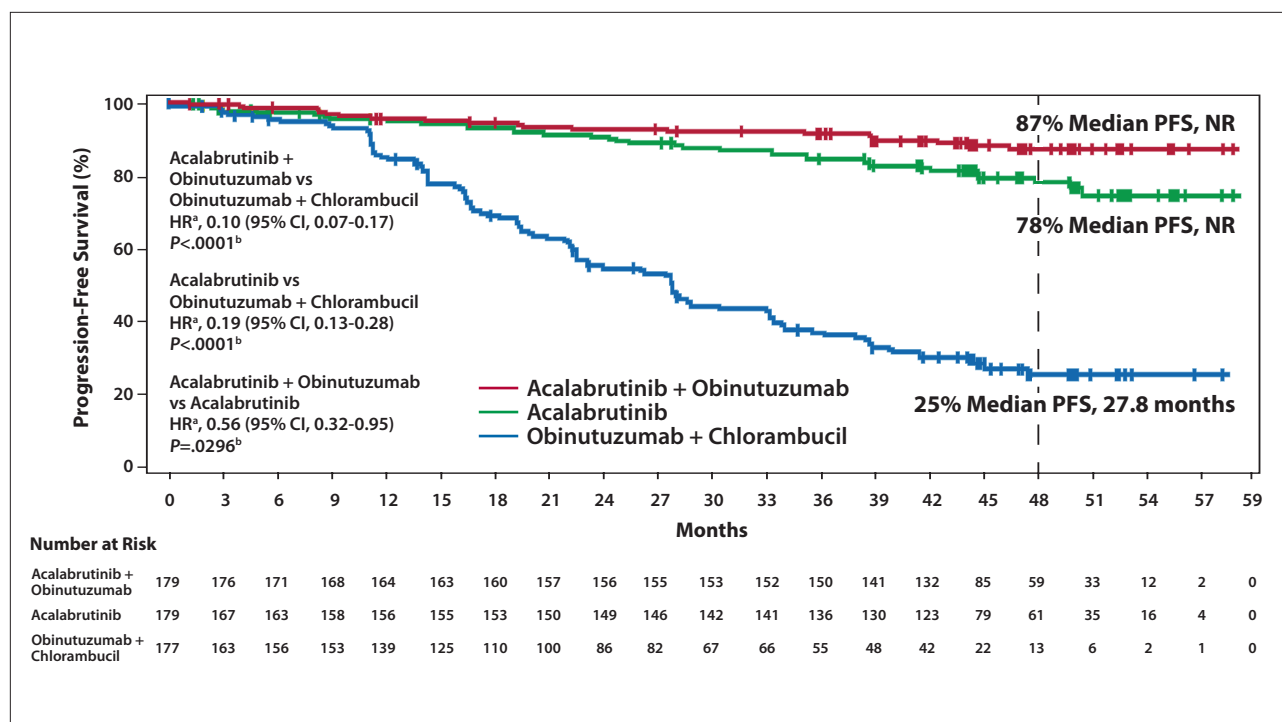


Figure 4. Estimated rates of progression-free survival as assessed by the investigator in a long-term analysis of the phase 3 ELEVATE-TN trial, which evaluated acalabrutinib monotherapy, acalabrutinib plus obinutuzumab, and obinutuzumab plus chlorambucil among patients with previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma. ^aThe hazard ratio was based on an unstratified Cox proportional hazards model. ^bThe *P* value was based on an unstratified log-rank test. HR, hazard ratio; NR, not reached; PFS, progression-free survival. Adapted from Sharman JP et al. ASCO abstract 7509. *J Clin Oncol.* 2021;39(15 suppl).²

stage III/IV disease. After a median follow-up of 28.3 months, the median PFS was superior with acalabrutinib monotherapy ($P<.0001$) and acalabrutinib plus obinutuzumab ($P<.0001$) vs chemoimmunotherapy.¹

A 4-year analysis was performed to provide data for longer-term safety and efficacy.² After a median follow-up of 46.9 months (range, 0-59.4 months), treatment discontinuation rates were 30.7% with single-agent acalabrutinib, 25.1% with acalabrutinib plus obinutuzumab, and 22.6% with chemoimmunotherapy. The median treatment exposure was 45.7 months, 46.6 months, and 5.6 months, respectively. Sixty-nine patients crossed over from the obinutuzumab/chlorambucil arm into the acalabrutinib monotherapy arm.

Consistent with results from the interim analysis, the longer follow-up showed that the median PFS was sig-

nificantly prolonged with acalabrutinib monotherapy (not reached; HR, 0.19; 95% CI, 0.13-0.28) and acalabrutinib plus obinutuzumab (not reached; HR,

0.10; 95% CI, 0.07-0.17) as compared with obinutuzumab plus chlorambucil (27.7 months).² At 48 months, the estimated rates of PFS were 78% with

ABSTRACT SUMMARY Herpes Zoster in Chronic Lymphocytic Leukemia: Effect of Vaccination and Treatment

A retrospective study assessed the impact of vaccination on rates of herpes zoster in patients with CLL using data from the Veterans Administration Central Cancer Registry (Abstract 7527). Among 7155 patients, 36.9% received first-line chemotherapy and 16.2% received second-line chemotherapy. Herpes zoster was identified in 1115 patients (15.6%). The rates of vaccination against herpes zoster prior to development of symptoms were 2.6% (29/1115) in patients who developed herpes zoster vs 8.6% (521/6040) in those who did not. Patients infected with herpes zoster were younger (68.0 vs 69.8 years; $P<.001$) and more likely to receive treatment for their CLL (58.1% vs 33.0%; $P<.001$). Patients with CLL who received first-line chemotherapy were at higher risk for developing herpes zoster (HR, 2.34; 95% CI, 2.02-2.71; $P<.001$). Receipt of second-line chemotherapy increased the risk for developing herpes zoster beyond that of first-line treatment (HR, 1.32; 95% CI, 1.13-1.55; $P<.001$).

acalabrutinib alone, 87% with acalabrutinib plus obinutuzumab, and 25% with obinutuzumab plus chlorambucil (Figure 4). Among patients with unmutated *IGHV*, the median PFS was significantly prolonged with acalabrutinib monotherapy (not reached) and acalabrutinib plus obinutuzumab (not reached) vs chemoimmunotherapy (22.2 months; $P < .0001$). The estimated 48-month PFS was 77% with acalabrutinib monotherapy, 88% with acalabrutinib plus obinutuzumab, and 4% with obinutuzumab plus chlorambucil. In patients with del(17p) or the *TP53* mutation, the median PFS was also not reached with acalabrutinib alone or in combination with obinutuzumab vs 17.7 months with obinutuzumab plus chlorambucil ($P < .005$).

The median OS was not reached in any of the arms; however, a trend was observed suggesting a potentially prolonged OS among patients treated with acalabrutinib plus obinutuzumab vs obinutuzumab plus chlorambucil

($P = .0604$).² The estimated 48-month OS rates were 88% with acalabrutinib monotherapy, 93% with acalabrutinib plus obinutuzumab, and 88% with obinutuzumab plus chlorambucil (Figure 5).

The ORR was significantly higher with acalabrutinib monotherapy compared with obinutuzumab plus chlorambucil (89.9% vs 82.5%; $P = .035$) and with acalabrutinib plus obinutuzumab compared with obinutuzumab plus chlorambucil (96.1% vs 82.5%; $P < .0001$).² The rate of CR/CRi with incomplete blood count recovery (CRi) was 30.7% with acalabrutinib plus obinutuzumab vs 13.0% with obinutuzumab plus chlorambucil. The rates of CR/CRi had increased at the 4-year analysis compared with the 28.3-month analysis, from 7.8% to 11.2% with acalabrutinib alone and from 24.0% to 30.7% with acalabrutinib plus obinutuzumab.

The most commonly reported AEs were generally the same as in the

earlier analysis.^{1,2} Most AEs in the acalabrutinib arms occurred during the first year of treatment. Any-grade AEs that were more common with acalabrutinib included headache, diarrhea, fatigue, arthralgia, cough, and upper respiratory tract infection. Any-grade AEs that were more common with chemoimmunotherapy included neutropenia, nausea, and infusion-related reaction.

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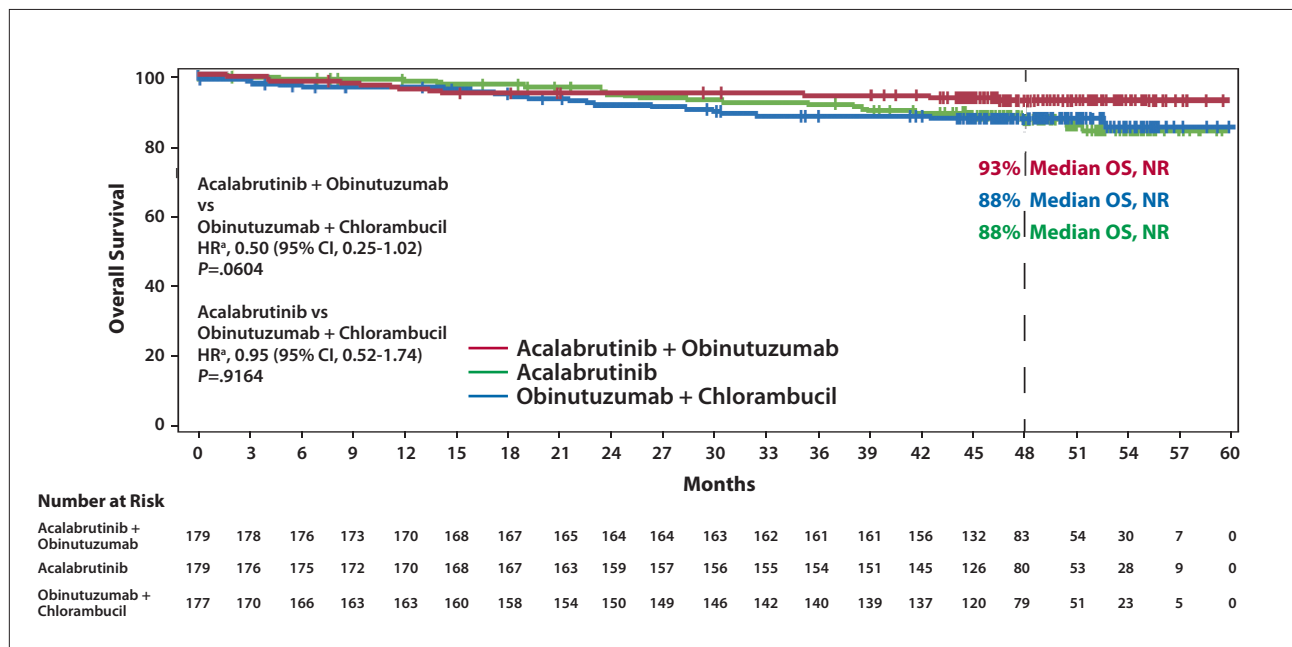


Figure 5. Estimated rates of overall survival in a long-term analysis of the phase 3 ELEVATE-TN trial, which evaluated acalabrutinib monotherapy, acalabrutinib plus obinutuzumab, and obinutuzumab plus chlorambucil among patients with chronic lymphocytic leukemia or small lymphocytic lymphoma. ^aThe hazard ratio was based on a stratified Cox proportional hazards model (stratified by del[17p] status). HR, hazard ratio; NR, not reached; OS, overall survival. Adapted from Sharman JP et al. ASCO abstract 7509. *J Clin Oncol*. 2021;39(15 suppl).²

Up to Seven Years of Follow-Up in the RESONATE-2 Study of First-Line Ibrutinib Treatment for Patients With Chronic Lymphocytic Leukemia

The international, open-label phase 3 RESONATE-2 trial compared ibrutinib vs chlorambucil as first-line therapy among patients with CLL/SLL who were ages 65 years or older and who required treatment.¹⁻³ Patients ages 65 to 69 years were enrolled if they had a comorbidity that precluded treatment with fludarabine, cyclophosphamide, and rituximab. Prior to randomization, the patients were stratified based on ECOG performance status and Rai stage. Ibrutinib was administered

at 420 mg once daily until disease progression or unacceptable toxicity. Chlorambucil was administered at 0.5 mg/kg, with escalation up to a maximum of 0.8 mg/kg, on days 1 and 15 of every 28-day cycle, for up to 12 cycles.

The trial enrolled 136 patients in the ibrutinib arm and 133 in the chlorambucil arm. The patients' median age was 73 years, and 35% had bulky disease. Among the evaluable patients, 58% (118/204) had unmutated *IGHV* and 22% (54/251)

had del(11q). After a median follow-up of 18.4 months, the median PFS was not reached with ibrutinib vs 18.9 months with chlorambucil (HR, 0.16; $P < .001$).² OS was also superior with ibrutinib vs chlorambucil, with estimated 24-month survival rates of 98% vs 85%.

At up to 7 years of follow-up, ibrutinib continued to yield superior outcomes compared with chlorambucil.⁴ The median PFS was not reached with ibrutinib vs 15.0 months with chlorambucil (HR, 0.160; 95% CI,

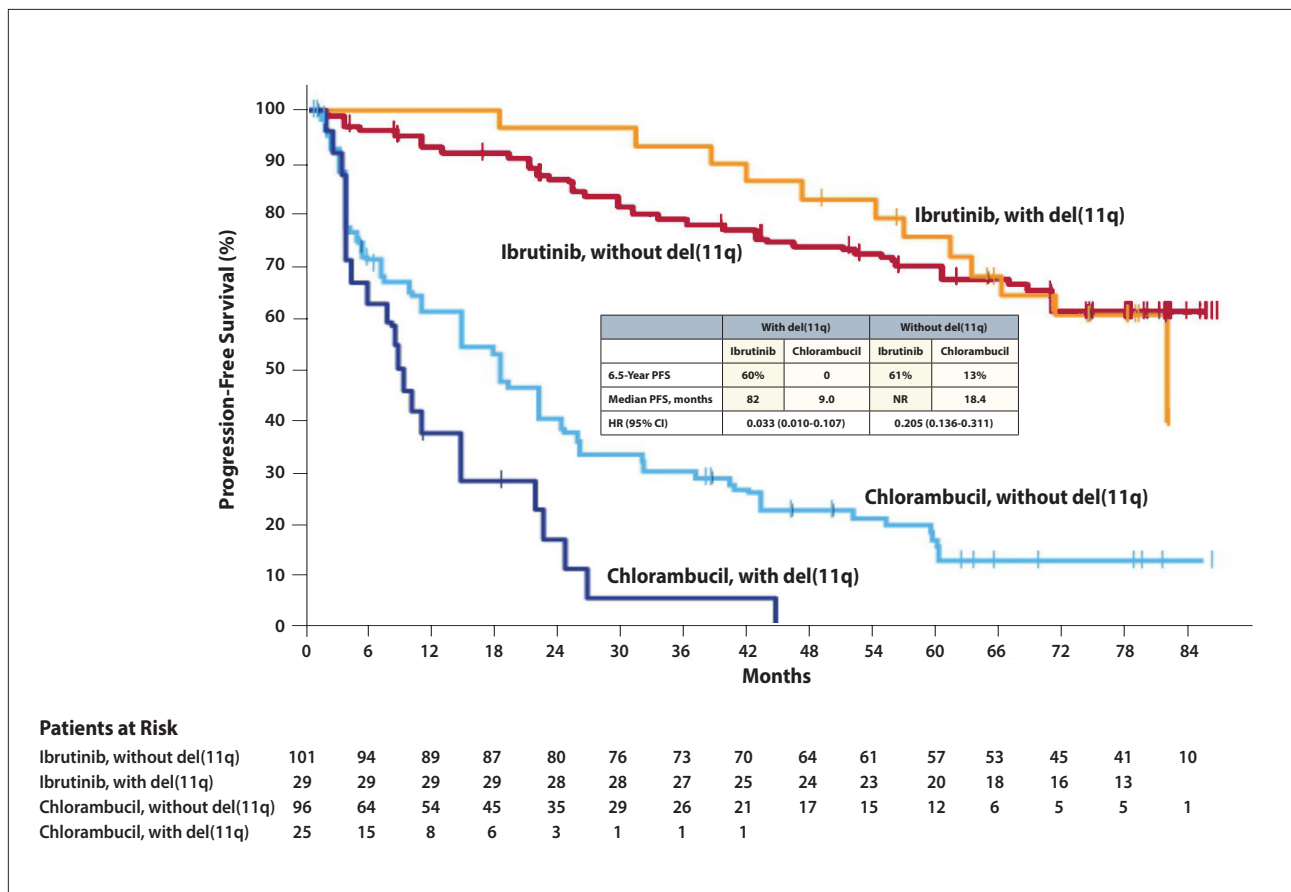


Figure 6. Progression-free survival according to del(11q) status in a long-term analysis of the phase 3 RESONATE-2 study, which compared ibrutinib vs chlorambucil as first-line therapy in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma who were older or unfit. del(11q), deletion 11q; HR, hazard ratio; NR, not reached; PFS, progression-free survival. Adapted from Barr P et al. ASCO abstract 7523. *J Clin Oncol.* 2021;39(15 suppl).⁴

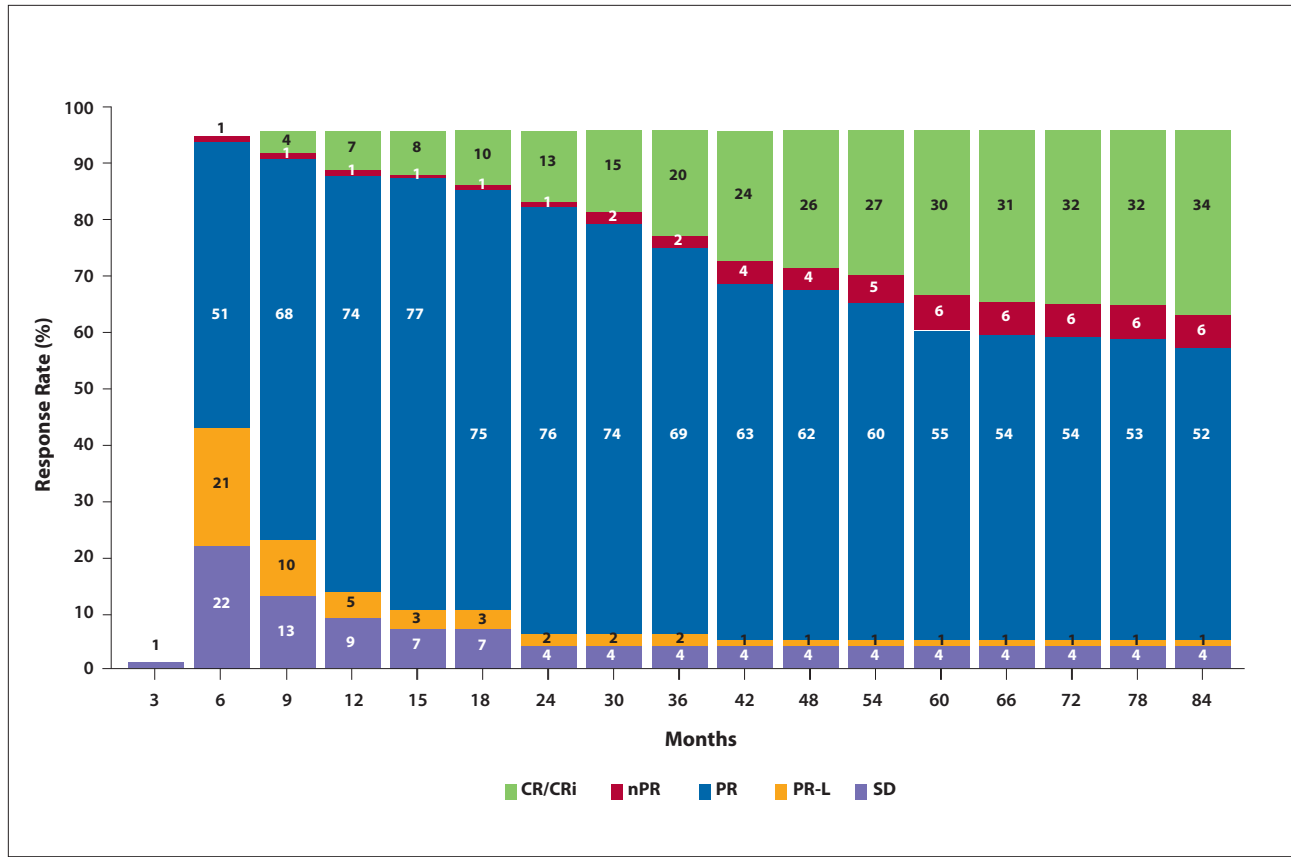


Figure 7. The overall response rate with ibrutinib according to the investigator in a long-term analysis of the phase 3 RESONATE-2 study, which compared ibrutinib vs chlorambucil as first-line therapy in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma who were older or unfit. CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease. Adapted from Barr P et al. ASCO abstract 7523. *J Clin Oncol.* 2021;39(15 suppl).⁴

0.111-0.230). At 6.5 years, 61% of ibrutinib-treated patients vs 9% of chlorambucil-treated patients were estimated to be alive and free of progressive disease. Among patients receiving active ibrutinib therapy, 12% developed progressive disease. Compared with chlorambucil, ibrutinib reduced the risk for disease progression or death in all patient subgroups, including those based on age, Rai stage disease, ECOG performance status, bulky disease, high-risk genetics, and level of β 2-microglobulin. Ibrutinib reduced the risk for disease progression or death by 97% in patients with del(11q) and by 89% in those with unmutated *IGHV*. In the ibrutinib arm, the median PFS was 82 months

in patients with del(11q) and not reached for those without del(11q); these durations were 9 months and 18.4 months, respectively, for patients treated with chlorambucil (Figure 6). PFS was similar among patients with mutated or unmutated *IGHV* who received ibrutinib.

At 84 months, treatment with ibrutinib led to an ORR of 92%, including a rate of CR/CR with incomplete bone marrow recovery of 34% (Figure 7). The median duration of response was not reached (range, <0.1-83 months). The estimated 5-year OS was 83% with ibrutinib vs 68% with chlorambucil. Ibrutinib was generally well tolerated, and no new safety signals were observed.

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First-in-Human Study of Lisoftoclax (APG-2575), a Novel BCL-2 Inhibitor, in Patients With Relapsed/Refractory CLL and Other Hematologic Malignancies

CLL/SLL, multiple myeloma, Waldenström macroglobulinemia, and other hematologic malignancies are characterized by overexpression of BCL-2, which confers resistance to apoptosis and thereby extends the survival of malignant cells.¹ Venetoclax is a BCL-2 inhibitor that is approved for the treatment of CLL/SLL. Treatment with venetoclax can lead to the development of tumor lysis syndrome, which can be fatal.² To avoid tumor lysis syndrome, venetoclax is administered with a “ramp-up” phase, in which the dose is gradually increased over 5 weeks. Venetoclax can also lead to thrombocytopenia and severe neutropenia.

Lisoftoclax (APG-2575) is a novel, potent, selective inhibitor of BCL-2 that disrupts the Bcl2/Bim complex and has demonstrated anticancer activity in preclinical models.³⁻⁵ The half maximal effective concentration (EC_{50}) of lisoftoclax was similar to that of venetoclax (1.952 nM vs 1.832 nM,

respectively) in a cell-free assay. In a cellular viability assay of a BCL2-driven acute lymphoblastic leukemia cell line, the EC_{50} was 0.003612 μ M for lisoftoclax vs 0.005317 μ M for venetoclax. The novel BCL-2 inhibitor was shown to disrupt the Bcl2/Bim complex in acute myeloid leukemia and acute lymphoblastic leukemia cells.

A first-in-human phase 1 study evaluated lisoftoclax among patients with previously treated CLL/SLL or another hematologic malignancy.³ The trial excluded patients who had received prior treatment with a BCL-2 inhibitor. Lisoftoclax was administered orally, once daily, in doses ranging from 20 mg to 1200 mg. The trial used a standard 3+3 design. Cohort A enrolled patients with hematologic malignancies other than CLL/SLL and a low risk for tumor lysis syndrome, and patients received a fixed dose of lisoftoclax on day 1 of cycle 1, without ramp-up. Cohort B enrolled patients with CLL/SLL at intermediate or

high risk for tumor lysis syndrome. Both cohorts enrolled 3 to 6 patients at each dose level. An accelerated dose-escalation strategy was followed until the dose level reached 400 mg or the patient developed a dose-limiting toxicity, any laboratory or clinical tumor lysis syndrome, any suspected hypersensitivity reaction, two grade 2 drug-related toxicities, or a single drug-related toxicity of grade 3 or higher. For both cohorts, additional expansion cohorts were planned based on the maximum tolerated dose, with enrollment of 9 to 12 patients. Study objectives included safety, efficacy, and pharmacokinetics.

The study enrolled 36 patients, whose median age was 70 years (range, 39-89 years).³ The most common cancer type was CLL/SLL (41.7%), followed by non-Hodgkin lymphoma (33.3%), multiple myeloma (16.7%), myeloid leukemia (5.6%), and hairy cell leukemia (2.8%). Patients had received a median of 2 prior therapies (range, 1-13). Treatment was discontinued in 21 patients (58.3%), most commonly owing to disease progression (13 of 21 patients). The most common treatment-related AEs, occurring in more than 15% of patients, were fatigue (27.8%), neutropenia (22.2%), diarrhea (19.4%), and anemia (16.7%). The most common AEs of grade 3 or higher included neutropenia (13.9%), nausea (5.6%), and platelet count decrease (5.6%). One patient discontinued therapy owing to a treatment-related AE, which consisted of grade 2 pruritus/skin sensitivity. No grade 5 treatment-related AEs occurred. No dose-limiting toxicities were observed with lisoftoclax at doses up to 1200 mg daily; thus, the maximum tolerated dose was not reached. No laboratory or clinical cases of tumor lysis syndrome

ABSTRACT SUMMARY Updated Results of the Selective Bruton Tyrosine Kinase Inhibitor TG-1701, as Monotherapy and in Combination With Ublituximab and Umbralisib (U2) in Patients With B-Cell Malignancies

TG-1701 is a BTK inhibitor that was evaluated as monotherapy and in combination with ublituximab and umbralisib in a dose-escalation trial (Abstract 7525). The 123 enrolled patients had CLL, Waldenström macroglobulinemia, or MCL. TG-1701 was administered in doses up to 400 mg daily. The maximum tolerated dose was not reached. Among 20 patients with CLL treated with TG-1701 (300 mg daily) as a single agent, AEs of grade 3 or higher included COVID-19 (10%), neutropenia (10%), increased alanine transaminase (5%), and increased aspartate transaminase (5%). Among these patients, the ORR was 100% after a median follow-up of 8.6 months (range, 2.5-10.7 months). Among the CLL patients treated with TG-1701 monotherapy at 200 mg daily, the ORR was 95%. The combination of TG-1701 with ublituximab and umbralisib was generally well tolerated, with the most common AEs of any grade being diarrhea, infusion-related reactions, and bruising, each occurring in 47% of patients.

were reported. The median duration of treatment was 6 cycles (range, 1-24 cycles). For cohort B, which included patients with an intermediate or high risk for tumor lysis syndrome, the recommended phase 2 dose of lisaftoclax was 600 mg daily.

Among the 15 patients with CLL/SLL, the median duration of treatment was 9 cycles (range, 5-24 cycles).³ A partial response was reported in 12 patients (80%) with CLL/SLL; no CRs occurred in this group of patients. The median time to response was 2 cycles (range, 2-8 cycles) in this cohort. Among the 21 patients diagnosed with

hematologic malignancies other than CLL/SLL, the median duration of treatment was 3 cycles (range, 1-22 cycles). A partial response was reported in 1 patient. There were no CRs.

A preliminary pharmacokinetic analysis showed a positive relationship between the administered dose of lisaftoclax and the plasma concentration of the drug.³ Lisaftoclax had a half-life of 4 to 8 hours. BH3 profiling in patient samples showed that lisaftoclax was associated with changes in Bcl2 proteins that were consistent with rapid reductions in absolute lymphocyte counts.

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Survival Trends in Chronic Lymphocytic Leukemia in the Era of Oral Targeted Therapies in the United States: SEER Database Analyses (1985 to 2017)

To evaluate the impact of targeted therapies on survival, a retrospective study compared estimated survival rates before vs after the introduction of targeted therapies for the treatment of patients with CLL. Survival data for these patients in the United States from 1973 to 2017 were

extracted from the Surveillance, Epidemiology, and End Results (SEER) database.^{1,2} The study included patients ages 15 years and older, with or without another subsequent cancer diagnosis. Five- and 10-year relative survival rates were estimated for patients treated from 1985 to 2017, based on their sex and

their age at diagnosis. Age groups were 15 to 44 years, 45 to 54 years, 55 to 64 years, 65 to 74 years, 75 to 84 years, and 85 years or older. Among patients diagnosed between 1985 and 2015, the proportion of long-term survivors based on sex and age was determined using a mixture cure model.³ HRs for death,

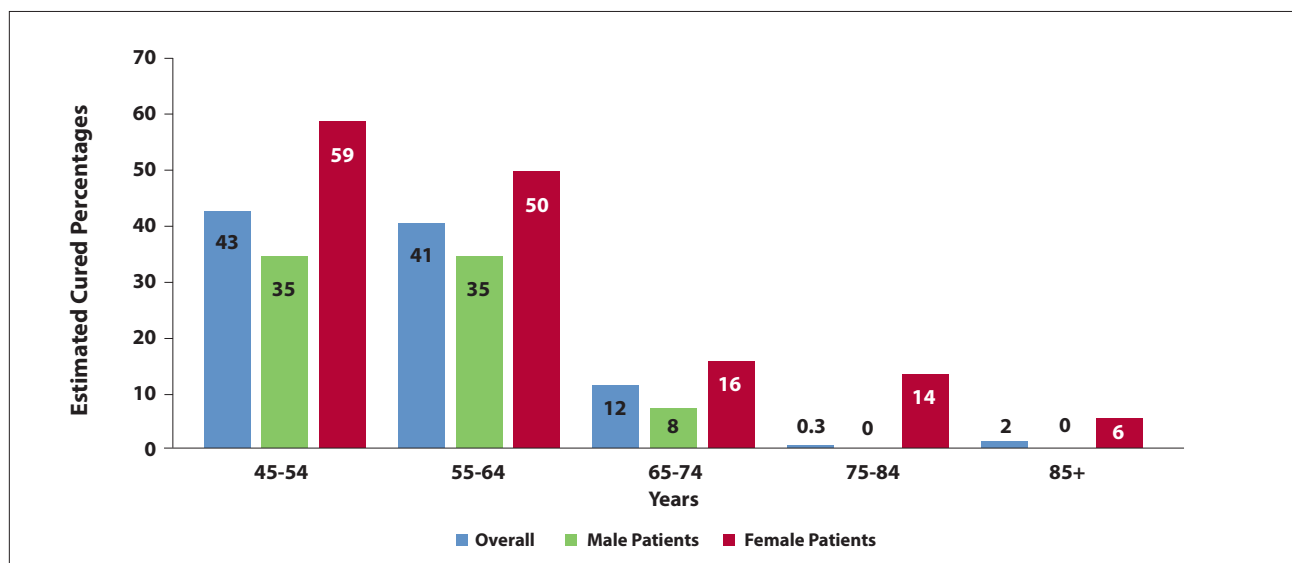


Figure 8. The estimated cured percentages according to age and sex among patients with chronic lymphocytic leukemia enrolled in a SEER database. SEER, Surveillance, Epidemiology, and End Results. Adapted from Alrawashdh N et al. ASCO abstract 7524. *J Clin Oncol*. 2021;39(15 suppl).¹

adjusted for sex and age at diagnosis, were calculated via Cox proportional hazard modeling for 2 cohorts. Cohort A included patients diagnosed between 2000 and 2003 and followed until 2012, and cohort B included those diagnosed between 2004 and 2007 and followed until 2015.

Among the entire study population, the 5-year relative survival increased from 73.7% in patients diagnosed between 1985 and 1989 to 89.4% in patients diagnosed between 2010 and 2014.¹ The 10-year relative survival in the same patient groups increased from 51.6% to 75%, respectively. For male patients, the 5-year age-adjusted relative survival rate increased from 72% in those diagnosed between 1985 and 1989 to 88% in those diag-

nosed between 2010 and 2014. For female patients diagnosed during the same periods, the 5-year age-adjusted relative survival rate increased from 76.8% to 90.8%. Among patients diagnosed between 1985 and 1989 vs those diagnosed between 2005 and 2009, 10-year age-adjusted relative survival rates increased from 47.3% to 72.5% for male patients and from 58.2% to 78.7% for female patients. The estimated cured percentages according to age and sex are shown in Figure 8.

For patients in cohort B compared with those in cohort A, the HR for death was 0.58 (95% CI, 0.43-0.78) for those ages 45 to 54 years, 0.58 (95% CI, 0.48-0.70) for those ages 55 to 64 years, 0.57 (95% CI, 0.49-0.67)

for those ages 65 to 74 years, 0.68 (95% CI, 0.54-0.85) for those ages 75 to 84 years, and 0.83 (95% CI, 0.0.68-1.02) for those ages 85 years or older.¹ Therefore, across all age cohorts, the risk of death was decreased in patients who were diagnosed between 2004 and 2007 compared with patients who were diagnosed between 2000 and 2003.

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Identification of Genetic Markers Associated With Ibrutinib-Related Cardiovascular Toxicity

Among patients with CLL, treatment with ibrutinib can be associated with cardiovascular AEs, such as atrial fibrillation and hypertension, that can lead to dose reduction and treatment discontinuation.¹ Such

toxicities likely result from off-target binding. A study of a single institutional database evaluated the molecular associations that led to cardiovascular AEs associated with ibrutinib therapy.² The patients had CLL and were treated

with ibrutinib between December 2019 and June 2020. All patients had started ibrutinib therapy at an initial dose of 420 mg daily, had completed at least 6 months of treatment or had experienced a cardiovascular AE within the first 6 months of treatment, and had provided consent to the specimen collection protocol. Patient charts were reviewed for demographic information, *IGHV* mutation status, disease cytogenetics, prior treatments, the initial dose and starting date of ibrutinib therapy, and drug-related AEs. DNA was isolated from buccal swabs and evaluated with next-generation sequencing for 40 single nucleotide polymorphisms (SNPs) in *GATA4*, *SGK1*, *KCNQ1*, *KCNA4*, *NPPA*, and *SCN5A*. A genetic risk score based on univariate analysis was developed to estimate the odds of cardiovascular AEs after adjusting for age, sex, and weight.

The study included 50 patients. Their median age was 72 years (range, 48-90 years).² Half of the patients received ibrutinib as first-line therapy.

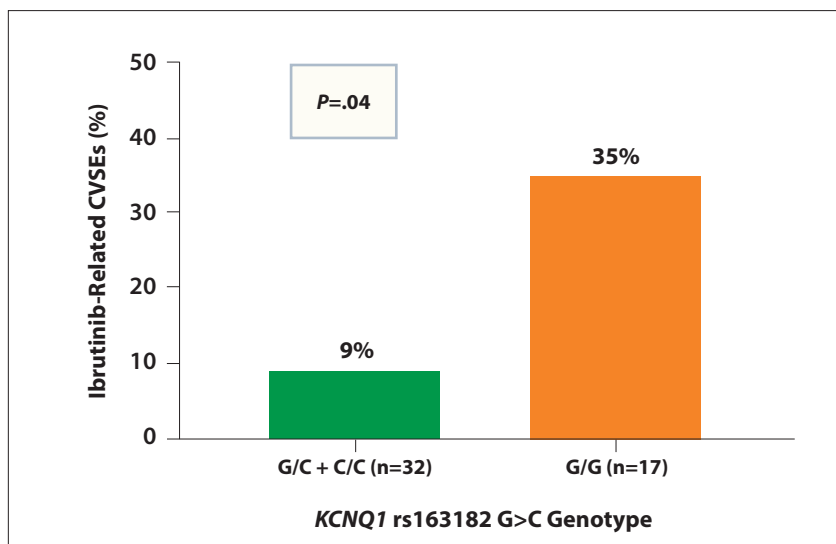


Figure 9. Rates of CVSEs related to ibrutinib among patients with chronic lymphocytic leukemia with the *KCNQ1* rs163182 G>C genotype. CVSEs, cardiovascular side effects. Adapted from Hamadeh I et al. ASCO abstract 7526. *J Clin Oncol*. 2021;39(15 suppl).²

Thirty patients (60%) were male. Ten patients (20%) developed a cardiovascular AE. After a median treatment duration of 16 months (range, 3-60 months), ibrutinib was discontinued in 4 of these patients (40%). Based on genetic profiling, the disease was considered low risk in 8 patients (16%) and high risk in 24 patients (48%). The median number of prior lines of therapy was 1 (range, 0-3).

In a univariate analysis, SNP genotyping showed that 2 SNPs in

KCNQ1 (Figure 9), 1 SNP in *GATA1*, and 1 SNP in *KCNA6* were significantly associated with cardiovascular AEs ($P \leq .05$).² Multivariate logistic regression analysis showed that patients harboring 2 or more of the identified SNPs had a significantly increased risk for developing a cardiovascular AE ($P = .02$). If these results can be confirmed in a larger study, the findings could be used to develop a genetic test for the presence of the identified polymorphisms in *GATA4*, *KCNQ1*,

and *KCNA5* in order to identify CLL patients who are at increased risk for developing a cardiovascular AE during treatment with ibrutinib.

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

The tyrosine kinase receptor known as ROR1 is expressed at high levels on many solid tumors and cancers of the blood, but it is not generally expressed in normal cells.¹ Cirmtuzumab (UC-961) is a humanized monoclonal antibody that inhibits the activity of ROR1.² A phase 1/2 study evaluated cirmtuzumab in

patients with relapsed or refractory mantle cell lymphoma (MCL) or CLL/SLL with radiographically measurable disease and an ECOG performance status of less than 3.³ The patients had radiographically measurable disease. Prior treatment with a BTK inhibitor was permitted. The trial used a conventional 3 + 3 design for dose escalation.

In the dose-escalation portion of the study, cirmtuzumab was administered at doses of 2 mg/kg, 4 mg/kg, 8 mg/kg, 16 mg/kg, 300 mg, and 600 mg; the first 5 doses were administered every 2 weeks and subsequent doses were administered every 4 weeks. Patients received daily ibrutinib therapy (500 mg daily for MCL patients; 420 mg

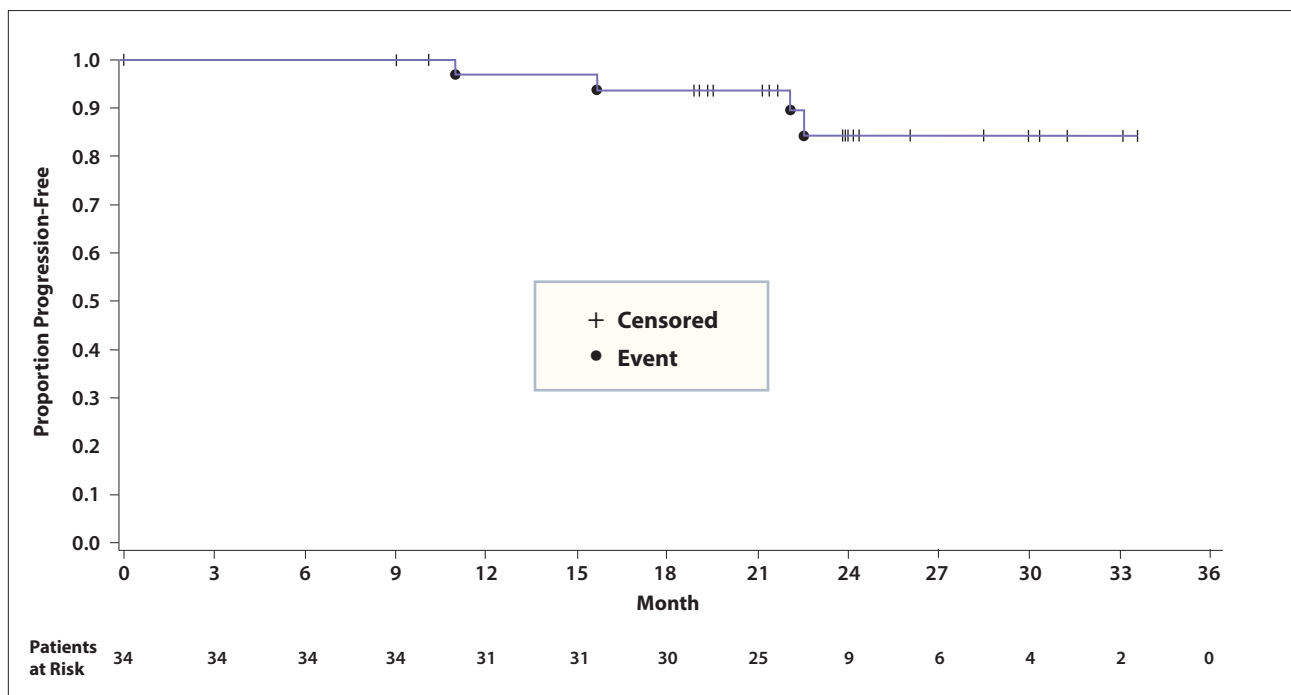


Figure 10. Progression-free survival among patients with chronic lymphocytic leukemia or small lymphocytic lymphoma who received cirmtuzumab and ibrutinib in a phase 1/2 trial. Adapted from Lee HJ et al. ASCO abstract 7556. *J Clin Oncol*. 2021;39(15 suppl).³

ABSTRACT SUMMARY Analyzing Treatment Patterns and Time to the Next Treatment in Chronic Lymphocytic Leukemia Real-World Data Using Automated Temporal Phenotyping

In an effort to optimize management strategies for patients with CLL, real-world treatment patterns and the time to next treatment (TTNT) were evaluated retrospectively using information from a single database (Abstract e19512). Among 411 patients, ibrutinib was the most common first-line treatment (40.8%), followed by anti-CD20-containing regimens (30.6%) and chemotherapy (19.2%). Acalabrutinib, venetoclax, and idelalisib were administered as first-line treatment in fewer than 5% of patients each. The TTNT of acalabrutinib was longer than that of ibrutinib. Compared with venetoclax, acalabrutinib had a longer median TTNT (742 vs 373 days; HR, 0.23; $P=.015$), as did ibrutinib (median TTNT, 598 vs 373 days; HR, 0.48; $P=.03$). Patients ages 65 years and older had a longer TTNT vs younger patients (HR, 0.16; $P=.016$).

daily for CLL patients) starting on day 1 of week 4.

The study enrolled 34 patients with CLL/SLL and 26 patients with MCL. In the CLL/SLL cohort, the median age was 68.0 years (range, 37.0-86.0 years).³ At baseline, 85.3% of these patients had Rai stage III/IV disease, and the median number of prior systemic therapies was 2 (range, 1-15). In the MCL cohort, the median age was 66.5 years (range, 45.0-85.0

years), and the median number of prior systemic therapies was 2 (range, 1-5).

Among 34 evaluable patients with CLL, the median follow-up was 22.1 months (range, 17.6-22.8 months).³ The ORR was 91.1%, with a CR rate of 14.7%. Among the 18 evaluable patients with MCL, the median follow-up was 8.5 months (range, 6.7-14.4 months). The ORR was 83.3%, with a CR rate of 38.9%. The median

duration of response was not estimable in the CLL cohort or the MCL cohort (95% CI, 11.93 months to not evaluable). The median PFS was not evaluable in CLL/SLL patients (Figure 10) or MCL patients.

The safety profile was similar to that observed in CLL patients treated with ibrutinib monotherapy.³ Among 88 patients in both cohorts who were evaluable for safety, the most common treatment-emergent AEs of any grade, regardless of causality, were contusion (37.5%), diarrhea (37.5%), and fatigue (36.4%). The most common AEs of grade 3 or higher included hypertension (10.2%) and fatigue (5.7%).

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Highlights in Chronic Lymphocytic Leukemia From the 2021 American Society of Clinical Oncology Annual Meeting: Commentary

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The 2021 American Society of Clinical Oncology (ASCO) annual meeting featured several important abstracts regarding the management of patients with chronic lymphocytic leukemia (CLL). New and updated clinical trial data were presented for treatments such as ibrutinib, acalabrutinib, and venetoclax.

Trends in Survival

An analysis of data from the Surveillance, Epidemiology, and End Results (SEER) database examined how survival has changed for patients with CLL from 1985 to 2017.¹ This study is a reflection of the advances in treatment for CLL. In the past, treatment had mainly consisted of chemotherapy with alkylating agents. Management evolved to encompass chemoimmunotherapy with monoclonal antibodies, followed by novel agents such as Bruton's tyrosine kinase (BTK) inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors, and BCL-2 inhibitors.

The trends have changed accordingly as the treatments improved. Between 1985 and 1989, the 5-year age-adjusted relative survival rate was 72% for male patients and 76.8% for female patients. From 2010 to 2014, these rates increased to 88.2% and 90.8%, respectively. This significant difference in outcomes reflects the improved management strategies now available. An even more illuminating comparison is the 10-year age-adjusted relative survival from diagnosis, which increased from 47% to 72% for male

patients and 58% to 78% for female patients. CLL is a generally incurable disease. Even throughout the longer period, survival trends have significantly improved, showing that patients in the current era have better outcomes with more therapeutic options, and can live longer.

Clinical Trials

Dr Paul Barr presented long-term follow-up of the open-label phase 3 RESONATE-2 study.² Earlier results of this important trial led to the approval of ibrutinib in the frontline setting.³ The trial compared treatment with continuous ibrutinib vs chlorambucil in patients with treatment-naïve CLL. The initial outcomes were very impressive. At a median follow-up of 18.4 months, the median progression-free survival (PFS) was not reached with ibrutinib vs 18.9 months with chlorambucil. A question was raised, however, about the toxicity that patients might experience during long-term treatment with ibrutinib. It was not known whether the toxicity would increase over time, or if new toxicity signals would arise.

The new analysis provided data for a median of 7 years of follow-up.² The PFS benefit was sustained for patients treated with ibrutinib vs chlorambucil, with a hazard ratio of 0.16 in favor of ibrutinib. At 6.5 years, the rate of PFS was 61% with ibrutinib vs 9% with chlorambucil. The median PFS was not reached in the ibrutinib arm vs 15.0 months in the chlorambucil

arm. This improvement was observed across all subgroups, including patients whose disease presented an unmutated immunoglobulin heavy chain variable (*IGHV*) gene or deletion 11q. The overall survival rate at 6.5 years was 78% with ibrutinib. At 5 years, the estimated overall survival rate was 83% with ibrutinib vs 68% with chlorambucil. The overall response rate was 92% for ibrutinib-treated patients, with complete response rates increasing to 34% (from 23% in the initial report).

This long-term analysis provides several insights. Patients who continue treatment with ibrutinib can have sustained remissions, and responses may deepen over time. An added benefit to this long-term follow-up analysis is that it showed no new safety signals. The rates of high-grade adverse events remained low, and they tended to decrease over time. The rate of grade 3 hypertension was 5% at 5 to 6 years of follow-up, and decreased to 4% after 6 to 7 years of follow-up. The rate of atrial fibrillation was 1% at 5 to 6 years of follow-up and also at 6 to 7 years of follow-up. There were no reports of major bleeding (grade 3 or higher) at 5 to 7 years of follow-up. Only 1% of patients required dose reductions during that period.

This analysis therefore shows that long-term treatment with ibrutinib is safe, and that most of the side effects tend to decrease over time. Treatment discontinuations, dose reductions, and major side effects tend to occur

in the beginning of treatment. This information was not known when ibrutinib was first used. These data are important because they show that patients can safely continue treatment with ibrutinib. When patients are able to get through the first 6 to 12 months of treatment, it is likely that they will be able to continue therapy safely for a longer period.

Dr Jeff Sharman presented data from an updated 4-year follow-up analysis of the phase 3 ELEVATE-TN trial, which evaluated acalabrutinib plus obinutuzumab, acalabrutinib monotherapy, and obinutuzumab plus chlorambucil among patients with treatment-naïve CLL.⁴ An interim analysis was initially published in 2020.⁵ The initial median follow-up was 28.3 months, and now the median follow-up is 46.9 months. Similar to the RESONATE-2 analysis, the aim of this long-term analysis was to evaluate if the improvement in outcomes seen with acalabrutinib with or without obinutuzumab persisted, and if any new safety signals arose.

In this study, obinutuzumab and chlorambucil were each administered for 6 months. Acalabrutinib was administered continuously. Patients in the obinutuzumab/chlorambucil arm who developed progressive disease were permitted to cross over to the acalabrutinib monotherapy arm.

The patients' median age was 70 years. The trial enrolled patients ages 65 years or older, as well as younger patients with comorbidities. The median follow-up was 46.9 months. The median PFS was still not reached for either of the acalabrutinib arms vs 27.8 months for the obinutuzumab/chlorambucil arm. The improvement was statistically significant for both acalabrutinib arms. Among patients with unmutated *IGHV*, who are at higher risk for disease progression, the median PFS was not reached for either of the acalabrutinib arms vs 22.2 months for the obinutuzumab/chlorambucil arm. Among patients

with the 17p deletion, the median PFS was not reached for either acalabrutinib arm vs 17.7 months for the obinutuzumab/chlorambucil arm. The complete response rates increased over time among patients who continued to receive acalabrutinib.⁴ This mirrors the results from the RESONATE-2 trial with ibrutinib,² again showing that disease response may deepen throughout prolonged exposure to BTK inhibitors.

This long-term analysis of the ELEVATE-TN trial identified no new safety signals with acalabrutinib.⁴ Most adverse events occurred in the beginning of treatment. There were no delayed significant side effects. The treatment discontinuation rates owing to adverse events were low, at approximately 12% for both acalabrutinib arms. There were low rates of disease progression. Most patients remained on treatment with acalabrutinib at the time of this analysis. In addition, the data are beginning to show a separation in the survival curve with a trend in favor of acalabrutinib plus obinutuzumab vs obinutuzumab plus chlorambucil; however, this difference is not yet statistically significant.

The study was not powered to compare acalabrutinib plus obinutuzumab vs acalabrutinib monotherapy. However, in a post hoc analysis of PFS, the hazard ratio was 0.52 in favor of the combination, with a significant *P* value. The true effect of this difference is not known because this retrospective post hoc analysis was not planned as part of the original trial design. The difference may indicate that a subset of patients may benefit from the addition of obinutuzumab, although at this point, it is not possible to identify who these patients might be. It appears that for patients with the 17p deletion or other markers of high-risk disease, there was no difference in the PFS curves between the acalabrutinib arms. With more follow-up, it may be possible to identify patients who may benefit from the addition of obinutuzumab to acalabrutinib.

This long-term analysis shows that acalabrutinib with or without obinutuzumab is very efficacious and safe. Importantly, the study shows no new safety signals, increasing response rates over time, and continued superiority of the acalabrutinib arms over the obinutuzumab/chlorambucil arm.

Dr John Byrd presented the first results of the phase 3 ELEVATE-RR trial, which is an important head-to-head trial of acalabrutinib vs ibrutinib.⁶ Ibrutinib was the first approved BTK inhibitor. Ibrutinib was safe and well tolerated in long-term analyses of clinical trials, such as RESONATE-2.² However, studies of real-world data have shown higher-than-expected discontinuation rates and higher rates of some adverse events than were reported in clinical trials.⁷ The question is whether these side effects are completely related to the mechanism of action of BTK inhibition, or whether they are possibly associated with off-target enzyme inhibition. Ibrutinib inhibits many other enzymes in addition to BTK. Newer BTK inhibitors have been developed with higher selectivity for this target enzyme. These second- and third-generation BTK inhibitors still present off-target enzyme inhibition, but at a much lower rate. The aim of the ELEVATE-RR trial was to identify whether ibrutinib and acalabrutinib differ in terms of the adverse events that are of concern with BTK inhibitors—mainly bleeding, atrial fibrillation, hypertension, and infections.

ELEVATE-RR was designed as a noninferiority trial.⁶ The primary endpoint was to show that efficacy was similar between ibrutinib and acalabrutinib. The study enrolled patients with high-risk CLL with deletion 17p or deletion 11q, whose disease had relapsed or was refractory to at least 1 prior line of treatment. A large population of patients (*N*=533) were randomly assigned to receive treatment with acalabrutinib or ibrutinib. Follow-up lasted a median of 40.9 months.

The trial followed a hierarchical secondary endpoint analysis. If the primary endpoint of noninferiority was met, then the first secondary endpoint would be the difference in rates of atrial fibrillation. If this difference was met, then the trial would move to the next endpoint, which was a difference in grade 3 infections, followed by rates of Richter transformation, and then overall survival. If at any point a secondary endpoint in the hierarchy was not met, the analysis of secondary endpoints would stop.

The median PFS was 38.4 months in both treatment arms. The lack of a difference therefore met the primary endpoint. The rates of atrial fibrillation significantly differed, at 9.4% with acalabrutinib vs 16% with ibrutinib ($P=.023$). Atrial fibrillation is a concern when prescribing BTK inhibitors. Knowing that acalabrutinib is equally efficacious as ibrutinib but is associated with lower rates of atrial fibrillation could help guide treatment selection. Depending on the patient's risk, acalabrutinib might be the preferred choice.

No differences were seen in grade 3 infection, so the analysis of secondary endpoints ended. There were also no differences in the rates of Richter transformation. The rates of all-grade hypertension were significantly different, at 9.4% with acalabrutinib vs 23.2% in ibrutinib. Grade 3 hypertension was reported in 4.1% of the acalabrutinib arm vs 9.1% of the ibrutinib arm. In my opinion, the difference in hypertension is very important, as in many cases, hypertension is difficult to control in patients who are receiving BTK inhibitors, who may require multiple anti-hypertensive medications to control hypertension. This difference may help guide treatment selection, particularly for patients who have preexisting hypertension, which afflicts a significant proportion of the CLL population.

The rate of bleeding events was 38% with acalabrutinib vs 51% in ibrutinib. However, the rate of major

bleeding events was similar between the arms, as was the rate of overall infections. Arthralgia and diarrhea are other side effects that can be particularly bothersome to patients, and the incidences were cumulatively lower in the acalabrutinib arm vs the ibrutinib arm. Headache is a well-known side effect of acalabrutinib and was significantly more common with acalabrutinib than ibrutinib. Headaches generally occur in the beginning of treatment, and tend to resolve after the first couple of months. In my experience, headaches can be successfully treated with caffeine and acetaminophen. However, headaches can be dose-limiting in some patients. In some cases, headaches can make treatment intolerable, and the patient may need to switch to an alternate therapy.

The ELEVATE-RR trial provided 2 main insights.⁶ First, it showed that a second-generation BTK inhibitor is as efficacious as a first-generation BTK inhibitor. Ibrutinib and acalabrutinib bind to the same site and have the same affinity for BTK. BTK inhibition is the driver of clinical efficacy, rather than off-target enzyme inhibition. It was important to see that prospective data showed no difference in their efficacy. Second, the trial showed a difference in the side effect profile. In this study, acalabrutinib appeared safer than ibrutinib. An adverse event led to treatment discontinuation in 14.7% of the acalabrutinib arm vs 21.3% of the ibrutinib arm.

This information might guide 2 aspects of treatment. The first is selection of a BTK inhibitor for patients in the clinic, and the second is selection of an agent as a component of combination regimens in future clinical trials. The biggest issue with BTK inhibitors administered as monotherapy is that they are supposed to be taken continuously. A goal with combination therapy would be to minimize the duration of treatment, perhaps by administering the BTK inhibitor for a shorter period. A BTK inhibitor might be combined

with novel therapies, such as a BCL-2 inhibitor, an anti-CD20 monoclonal antibody, or even a PI3K inhibitor. These drugs are efficacious on their own. The main concern is added side effects when they are combined. For future combination regimens, there is the possibility that acalabrutinib might be the superior choice because it is better tolerated than ibrutinib.

Another very important study presented at the ASCO meeting was the phase 2 CAPTIVATE trial, which evaluated the combination of ibrutinib and venetoclax.⁸ This analysis focused on a cohort of treatment-naïve patients with CLL, who received a fixed-duration regimen. (A previous report of the study provided data for a different cohort of patients, who received treatment for 15 months and then were randomly assigned to maintenance therapy based on minimal residual disease [MRD] status.⁹) Patients in the fixed-duration cohort first received 3 cycles of ibrutinib as a single agent. Then venetoclax was added with the usual ramp-up over 5 weeks. Patients received 12 cycles of the combination regimen. Altogether, the patients received 15 cycles of treatment. The primary endpoint was complete response, including complete response with incomplete bone marrow recovery. The secondary endpoints were objective response rate, duration of response, levels of undetectable MRD at a sensitivity of 10^{-4} , PFS, overall survival, reduction in tumor lysis risk, and safety.

The trial enrolled 159 patients. Their median age was 60 years, which is somewhat younger than the general CLL population, but still reflective of patients seen in the clinic. Some of the patients presented with disease that had high-risk features, including 17% with deletion 17p or *TP53* mutation, 18% with deletion 11q, and 19% with complex karyotypes. Some physicians who treat CLL still advocate that patients with very high-risk cytogenetics might benefit from

continuous therapy rather than fixed-duration therapy with the agents currently available, as these patients present with higher rates of progression once treatment is discontinued.^{10,11} In the CAPTIVATE trial, however, that trend seems to have been reversed.⁸

Patients were enrolled in the study and followed for a median of 28 months.⁸ The complete response rate was 55%. The response rate was consistent across all of the high-risk subgroups. Among the patients who achieved a complete response, in 89%, the response persisted for more than a year. This observation is interesting because it shows that the response was sustained after planned discontinuation of therapy. Among the entire population, including patients with a partial response, the rates of undetectable MRD were 77% in the peripheral blood and 60% in the bone marrow.

Other studies have suggested that undetectable MRD is linked to durability of response and PFS,^{12,13} although this area is still under investigation. It is also not known yet if levels of undetectable MRD should guide discontinuation of treatment. In the CAPTIVATE trial, the 24-month PFS was 95%.⁸ At 12 months after discontinuation of treatment, most patients still had not presented with progression of disease. The 24-month overall survival was 98%.

These results were similar for patients without deletion 17p. Importantly, the results were maintained among patients with the 17p deletion or the *TP53* mutation. The complete response rate in this population was 56%, and the 24-month PFS was 84%. The rate of undetectable MRD in patients carrying the 17p deletion or the *TP53* mutation was 81% in the blood and 41% in the bone marrow. The CAPTIVATE trial therefore showed that the majority of patients, including those with high-risk disease, did not develop progressive disease in the year after treatment was discontinued. The data suggest that for patients

with high-risk disease, the combination of ibrutinib and venetoclax as a fixed-duration regimen is safe and leads to sustained control of the disease.

There were no cases of tumor lysis syndrome in the CAPTIVATE trial, which reflects the use of 3 months of ibrutinib induction therapy before venetoclax.⁸ The rate of adverse events was low, and most events were grade 1 or 2. The most common grade 3/4 adverse event was neutropenia, which occurred in 33% of patients. Grade 3/4 hypertension was reported in 6% of patients. The rates of treatment discontinuation were low: 4% of patients discontinued ibrutinib and 2% discontinued venetoclax.

A caveat to the interpretation of these data is that CAPTIVATE was a single-arm phase 2 study.⁸ It did not compare treatments, so the results are hypothesis-driving. The question that CAPTIVATE answers best concerns safety. The data showed that it is safe to combine ibrutinib and venetoclax. Data from the phase 3 GLOW trial were presented at the 2021 European Hematology Association congress.¹⁴ The GLOW trial compared ibrutinib plus venetoclax vs obinutuzumab plus chlorambucil, showing a superiority in favor of the novel agent combination. However, at this point, obinutuzumab plus chlorambucil should no longer be the comparator of choice, given the known superiority of other agents over this combination. These trials do not yet answer the question of whether a combination of a BTK inhibitor with a BCL-2 inhibitor is superior to either of these agents alone or in combination with a monoclonal anti-CD20 antibody.

Future Research

The field is moving toward combining agents in fixed-duration regimens. Ongoing trials are also evaluating whether MRD can guide treatment duration.^{15,16} We need to understand how to best identify the small percentage of patients who will develop pro-

gressive disease early after treatment discontinuation, and if it is valid to continue treatment for longer periods in this subset.

Disclosure

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